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[Intervention Review]

Antigen-specific active immunotherapy for ovarian cancer

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ABSTRACT

Background

Despite advances in chemotherapy, prognosis of ovarian cancer remains poor. Antigen-specific active immunotherapy aims to induce a tumour-antigen-specific anti-tumour immune responses as an alternative treatment for ovarian cancer.

Objectives

To assess feasibility of antigen-specific active immunotherapy for ovarian cancer. Primary outcomes are clinical efficacy and antigen-specific immunogenicity with carrier-specific immunogenicity and side-effects as secondary outcomes.

Search methods

A systematic search of the Cochrane Central Register of Controlled Trials (CENTRAL) Issue 3, 2009, Cochrane Gynaecological Cancer Group Specialized Register, MEDLINE and EMBASE databases and clinicaltrials.gov was performed (1966 to July 2009). Hand searches were conducted of the proceedings of relevant annual meetings (1996 to July 2009).

Selection criteria

Randomised controlled trials (RCTs), as well as non-randomised non-controlled studies that included patients with epithelial ovarian cancer, irrespective of stage of disease, and treated with antigen-specific active immunotherapy, irrespective of type of vaccine, antigen used, adjuvant used, route of vaccination, schedule, and reported clinical or immunological outcomes.

Data collection and analysis

Data extraction was performed independently by two review authors. Risk of bias was evaluated with the Delphi-list for RCTs or a selection of quality domains pivotal to the assessment of non-RCTs and deemed best applicable to the non-randomised non-controlled studies.

Main results

Thirty-six studies were included. Response definitions showed substantial variation between trials, which makes comparison of trial results unreliable. Information on adverse events was frequently limited. Furthermore, reports of both RCTs and non-RCTs frequently lacked information necessary to assess risk of bias. Serious biases in these trials can thus not be ruled out.

The largest body of evidence is currently available for CA-125 targeted antibody therapy (15 studies: 1505 patients). Non-RCTs of this CA-125 targeted antibody therapy suggest increased survival in humoral and/or cellular responders. However, three large randomised placebo-controlled trials did not show any clinical benefit despite induction of immune responses in approximately 60% of patients.

Other small studies targeting many different tumour antigens showed promising immunological results. As these strategies have not yet been tested in RCTs, no reliable inferences about clinical efficacy can be made. Given the promising immunological results, limited side effects and toxicity exploration of clinical efficacy in large well-designed RCTs may be worthwhile.

Authors' conclusions

We conclude that despite promising immunological responses no clinically effective antigen-specific active immunotherapy is yet available for ovarian cancer. Furthermore, the adoption of guidelines to ensure uniformity in trial conduct, response definitions and trial reporting is recommended to improve quality and comparability of immunotherapy trials.

PLAIN LANGUAGE SUMMARY

Antigen-specific active immunotherapy for ovarian cancer

Epithelial ovarian cancer is the most frequently diagnosed ovarian malignancy and the leading cause of death from gynaecological cancers. Standard therapy consists of surgery followed by chemotherapy. Although initial response rates are high, the majority of patients with advanced disease relapse. No curative treatment is available for recurrent disease. The observation that the presence of certain immune cells in tumours is associated with improved survival, suggests that stimulation of anti-tumour immune responses, i.e. immunotherapy, might be a useful approach to improve prognosis of ovarian cancer. In this review, the feasibility of antigen-specific active immunotherapy is evaluated. Antigen-specific active immunotherapy aims at the induction of tumour-directed immune responses through the administration of a tumour-antigen, a molecule that is preferentially expressed by tumour cells and can induce immune responses. As immunotherapy is a novel treatment strategy early phase studies were also included. Information on clinical and immunological responses, and adverse events was collected.

Thirty-six studies, which included 1780 ovarian cancer patients, were identified between 1966 and 2009. The most frequently described strategy (1505 patients in 15 studies) was administration of antibodies targeting CA-125. Most of these primarily evaluated safety and immunological responses. Five studies described severe flu-like and gastro-intestinal symptoms in 7 to 30% of patients. Antibodies and immune cells recognising CA-125 were frequently detected, albeit response rates varied between studies. Despite promising immunological responses, three large studies found equal survival rates for patients treated with placebo or CA-125 directed antibody. Because there is currently no high quality evidence of clinical benefit, antibody therapy targeting CA-125 should in its current form not be incorporated in standard treatment.

For strategies not relying on antibody administration, similar conclusions cannot be drawn as these have not yet been tested in large trials to evaluate clinical efficacy of treatment. These were generally small studies primarily investigating vaccine safety and immunogenicity. Overall, treatment was well-tolerated, with inflammatory side effects at injection site most frequently reported. Antibodies and immune cells were induced by most strategies studied, but their clinically efficacy still has to be evaluated in large trials.

Based on a lack of uniformity in included studies, we strongly advocate universal adoption of response definitions, guidelines for adverse events reporting, and directives for trial conduct and reporting. Furthermore, results from ongoing RCTs should be awaited and furhter RCTs should be conducted.

BACKGROUND

Description of the condition

Ovarian cancer is the sixth most common cancer and the seventh cause of death from cancer in women worldwide (Parkin 2006). It is the second most common gynaecological cancer and the leading cause of death from gynaecological cancers in the Western world. As the majority of ovarian malignancies (80 to 90%) arise from the epithelium, all statements in the remainder of this review about ovarian cancer apply to epithelial ovarian cancer only. World-wide age standardized incidence rates range from 2.6 per 100,000 in Northern Africa to 13.3 per 100,000 in Northern Europe (Parkin 2006).

Stage of disease at presentation is the most important prognostic factor. Due to the asymptomatic course of disease, the majority of patients have extensive disease at presentation (stage III to IV according to FIGO classification (Benedet 2000)). Despite standard treatment, which consists of cytoreductive surgery and platinum-based chemotherapy, almost all patients with advanced stage disease at presentation will relapse, with a median progression free survival (PFS) of only 18 months. When residual or recurrent disease manifests itself, resistance to chemotherapy often prohibits further curative therapy, resulting in a disease specific five-year survival for patients with advanced stage ovarian disease of only 10 to 20% (Agarwal 2006; Thigpen 2000).

Description of the intervention

The immune system seems to play a role in ovarian cancer. This is reflected in the observation that in more than half of ovarian cancer patients, T- cells are present within tumour-islets (Raspollini 2005; Zhang 2003). Patients with advanced ovarian cancer, whose tumour is infiltrated by these T-cells, have a better clinical outcome compared to patients without these tumour-infiltrating T-cells (Dong 2006; Raspollini 2005; Zhang 2003). More specifically, higher numbers of cytotoxic T-cells, which can directly recognise and kill tumour cells, and increased ratios between cytotoxic T-cells ($CD8^+$) and helper T-cells ($CD4^+$) within the tumour epithelium are associated with improved survival (Sato 2005).

Immunotherapy is one of the novel therapeutic strategies under investigation for ovarian cancer. It aims to induce or enhance active immune responses directed towards the tumour and to consolidate anti-tumour effects of standard therapy, delay and possibly prevent progression of disease. More specifically, antigen-specific active immunotherapy aims at activation of the adaptive immune system directed towards a specific target antigen through administration of a molecular defined antigen-specific vaccine to the patient.

How the intervention might work

An antigen is a molecule, usually a protein or polysaccharide, which can stimulate an immune response. Tumour antigens can be subdivided into different categories such as mutated self proteins, products of oncogenes (e.g. Her-2/Neu), mutated tumour suppressor genes (e.g. p53), and aberrantly expressed self proteins (e.g. sperm protein 17, MAGE-1). Numerous tumour-associated antigens are known in ovarian cancer. To obtain a tumour-specific immune response, immunotherapy exploits the differential expression of antigens between normal and tumour cells. A major challenge concerning the safety of immunotherapy lies in the prevention of auto-immunity i.e. induction of immune cells that preferentially recognise and kill tumour cells, but avoid destruction of normal body cells. From a theoretical point of view, other possible side effects include allergic reactions to components of the vaccine and inflammatory reactions at the site of injection.

Why it is important to do this review

Several immunotherapeutic strategies are now being employed using different tumour antigens. These studies have, however, generally not yet evolved past phase I/II studies. To our knowledge, no systematic review of antigen-specific active immunotherapy in ovarian cancer has been carried out so far.

The immunogenicity and clinical efficacy of antigen-specific active immunotherapy in ovarian cancer is evaluated in this review. A systematic review about this topic is useful to ascertain the achievability of this treatment modality for ovarian cancer.

OBJECTIVES

The primary objective of this review was to assess the efficacy (i.e. clinical and/or immunological responses) of antigen-specific active immunotherapy for the treatment of ovarian cancer. The secondary objective was to establish which immunotherapeutic strategies combined with which tumour antigens provide the best immunological and clinical results.

METHODS

Criteria for considering studies for this review

Types of studies

We anticipated that there would be no RCTs on this subject. Therefore we also included phase I, phase II non-randomised and

non-controlled and if available phase III studies. We realised that results from non-randomised non-controlled studies cannot readily be extrapolated to the general population. Nevertheless, we felt that given the anticipated lack of RCTs, inclusion of these studies into this review was justifiable.

Types of participants

Women diagnosed with epithelial ovarian cancer, irrespective of stage of disease. However, as patient populations may differ substantially between different types of studies to be included in this review, for each study we documented what type of patient was included into the study (e.g. patients with end-stage disease or patients with residual disease).

Because we anticipated that there would not be many studies which included patients with ovarian cancer only, we also included immunotherapeutic studies in cancer patients that included at least two patients with ovarian cancer; with the additional requirement that the results for these individual patients were separately identifiable from the study publication or communication with the author and only data on these patients were extracted for the review. We were fully aware of the vigilance necessary when drawing conclusions based on studies with such small numbers, but felt that given the anticipated lack of large RCTs, inclusion of these studies into this review was justifiable.

Types of interventions

Antigen-specific active immunotherapy is defined as therapy which aims at inducing an adaptive immune response directed towards the tumour by means of administration of a specific well-defined tumour antigen. We compared interventions with each other based on the above-mentioned characteristics.

We included all interventions that aimed at antigen-specific active immunotherapy irrespective of type of vaccine, antigen used, adjuvant used, route of vaccination, vaccination schedule.

Types of outcome measures

Primary outcomes

Clinical efficacy

To assess clinical efficacy we evaluated:

1. Tumour responses to immunotherapy (complete/partial response, stable/progressive disease), as measured by:

- CA-125 levels according to or transposable to Gynecologic Cancer Intergroup (GCIG) criteria (Rustin 2004)
- Tumour response according to WHO criteria (WHO 1979) or Response Evaluation Criteria in Solid Tumors Group (RECIST) criteria (Therasse 2000)

2. If available we evaluated responses to post-immunotherapy treatment, as there are indications in small cell lung cancer that patients treated with chemotherapy after immunotherapy have increased survival as opposed to patients who did not receive immunotherapy (Antonia 2006).

3. If available, survival differences based on treatment with immunotherapy.

Antigen-specific immunogenicity

We recorded the number of observed antigen-specific humoral and cellular responses. When possible, we separately reported responses of cytotoxic ($CD8^+$) T-lymphocytes and/or helper ($CD4^+$) T-lymphocytes.

Secondary outcomes

Carrier-specific immunogenicity

As certain immunotherapeutic strategies rely on the use of carriers that may be the subject of an immune response besides the intended antigen-specific immune response, we recorded information on the induction of carrier-specific immune responses when appropriate.

Adverse events

To obtain imformatiojn on the toxicity of antigen-specific immunotherapy, we extracted data on adverse events observed and reported in the different studies. Adverse events were categorised as local adverse events at the site of immunisation or systemic adverse events (all other reported adverse events). Systemic adverse events were subdivided into autoimmunity, allergic reactions and other adverse events occurring after immunisation.

Search methods for identification of studies

Cochrane Central Register of Controlled Trials (CENTRAL) Issue 3, 2009, Cochrane Gynaecological Cancer Group Specialized Register as well as the prospective trial register www.clinicaltrials.gov were searched. Furthermore, we searched MEDLINE (1966 to July 2009) and EMBASE (1974 to July 2009) according to the search strategies listed in Appendix 1 and Appendix 2.

Hand searching was undertaken of abstracts in the proceedings of annual meetings of Society of Gynecologic Oncologists, the American Association for Cancer Research and the International Society for Biological Therapy of Cancer (1996 to July 2009).

The bibliography of each primary reference and of recent reviews of immunotherapy for ovarian cancer was checked for additional study publications. In addition we wrote to specialists involved in research regarding immunotherapy for ovarian cancer for information about the results of unpublished or ongoing studies. Relevant data were included in this review.

There were no language restrictions other than those inherent to the databases surveyed.
The search strategies used have been developed and executed by the author team.

Data collection and analysis

Selection of studies

All titles and abstracts retrieved by electronic searching were downloaded to Reference Manager, duplicates were removed and the remaining references were examined by two review authors (HWN and NL) independently. Those studies which clearly did not meet the inclusion criteria were excluded and copies of the full text of potentially relevant references were obtained. The eligibility of retrieved papers was assessed independently by two review authors (HWN and NL). Differences between review authors were resolved by discussion or by appeal to a third review author if necessary (TD). Reasons for exclusion were documented.

Data extraction and management

For included studies, data on characteristics of patients and interventions, study quality and endpoints were extracted independently by two review authors (HWN and NL) onto a data extraction form specially developed for the review (Appendix 4).
Where data on clinical efficacy and antigen-specific immunogenicity were missing from reports, we attempted to contact the authors to obtain the missing information. Results were checked for accuracy by a third review author (WH or TD).

Assessment of risk of bias in included studies

Risk of bias in RCTs complying with our selection criteria were assessed according to the Delphi-list (Verhagen 1998). Studies were evaluated based on randomisation, concealment of treatment allocation, blinding of patient, caregiver and outcome assessor, baseline similarity of groups, intention-to-treat (ITT) analysis, specification of eligibility criteria, and presentation of point estimates and measures of variability for the primary outcome measures.
No standard tools to evaluate validity are available for non-RCTs. Instead, for these studies we evaluated the risk of bias using the following four domains (Table 1):

- sample definition and selection
  - clear definition of inclusion / exclusion criteria
  - representative selection
  - adequate description of baseline characteristics
- interventions:
  - clear specification
  - concurrent / concomitant treatment
- outcomes:
  - specifications of outcome measures
  - relevance of outcome measures
  - reporting of outcome measures
- statistical analysis:
  - adequate rationale for number of patients included
  - adequate description withdrawal / exclusion during the study
  - adequate presentation of results.

These domains were selected as representative for and applicable to non-randomised non-controlled studies from a list of 12 quality domains and items deemed to be pivotal to the assessment of non-RCTs (Deeks 2003).
Risk of bias assessment was carried out by two review authors (HWN and NL). Discrepancies between review authors were be solved by discussion; if necessary a third author (WH or TD) was consulted.

Data synthesis

This review provides a narrative analysis, because the included studies are highly heterogenous regarding intervention and outcome measures. Furthermore data in publications were often presented with insufficient details (lack of standard deviations (SDs) or only some of the multiple outcomes presented), and additional information from report authors was difficult to obtain. Therefore we felt that quantitative meta-analysis and calculation of effect size estimates would neither be meaningful nor appropriate in this review. We limited analysis to a structured summary and discussion of available studies and findings.

RESULTS

Description of studies

Results of the search

From the electronic searches of MEDLINE and EMBASE, 56 out of 311 abstracts were selected as potentially compliant with the selection criteria and full texts were retrieved. Evaluation of the retrieved full texts resulted in the exclusion of 26 papers (see Excluded studies). In addition to the 30 selected full texts, another 14 abstracts were identified by hand searching the proceedings of the periodic meetings specified in the methods section. Authors were contacted for manuscripts, but no full texts were obtained for these abstracts. Together the 44 selected full texts and meeting abstracts described a total of 35 studies. Search of the prospective trial register www.clinicaltrials.gov resulted in identification of an additional 26 studies. For only four of these a full text or meeting abstract could be retrieved and only one study complied with our inclusion criteria (Sabbatini 2007). The remaining studies were

either ongoing (n = 15) or completed but not yet published (n = 6). Search of CENTRAL (Issue 3, 2009) did not identify any additional studies. Thus a total of 36 studies were included in this review. Generally, the most recent peer-reviewed publication was selected as the primary reference.

Included studies

The 36 studies included in this review were all published in English (Characteristics of included studies, Table 2).

Design

As expected the majority of studies were uncontrolled phase I or II studies (27 out of 36). Only three studies were randomised placebo controlled studies (Berek 2001; Berek 2004; Berek 2009). Randomised allocation of patients to different regimens was used in six studies (Braly 2009; Chu 2008; Freedman 1998; Herrin 2007; Method 2002; Sabbatini 2006). In four studies the immunogenicity of a previously applied immuno scintigraphic agent was retrospectively studied (Möbus 2003; Noujaim 2001; Schultes 1998; Wagner 1993).

Sample sizes

The median number of patients treated per study was 20 (range 2 to 371). Nine studies included less than ten patients. Six studies also included patients with other types of cancer (Brossart 2000; Gulley 2008; Mohebtash 2009; Sandmaier 1999; Ströhlein 2009; Tsuda 2004). A sample size calculation or rationale was provided for six studies only (Berek 2004; Berek 2009; Braly 2009; Leffers 2009a; Sabbatini 2006; Sabbatini 2007).

Participants

As was expected, the disease status at study entry varied largely between studies. Patients with evidence of residual or recurrent disease after treatment were most frequently included (13 out of 36) (Freedman 1998; Gulley 2008; Leffers 2009a; Ma 2002; Method 2002; Mohebtash 2009; Nishikawa 2006; Pfisterer 2006; Reinartz 2004; Sandmaier 1999; Schultes 1998; Ströhlein 2009; Wagner 1993). Four studies included patients with and without evidence of disease after prior therapy (Braly 2009; Chianese-Bullock 2008; Odunsi 2007; Tsuda 2004). Eight studies included patients with complete response to therapy for primary or recurrent disease (Berek 2001; Berek 2004; Berek 2009; Chu 2008; Diefenbach 2008; Odunsi 2007a; Sabbatini 2000; Sabbatini 2007). In addition, one study also included patients with minimal residual disease after primary therapy (Sabbatini 2006). In one study treatment was administered together with adjuvant chemotherapy after primary cytoreductive surgery (Braly 2009). For the remaining nine studies disease status at entry was not reported.

Interventions

The majority of studies described antibody therapy (18 out of 36), usually targeting CA-125 (15 out of 18). Most studies included only one target antigen in the vaccine, but in six studies multiple antigens were simultaneously targeted (Chianese-Bullock 2008; Chu 2008; Gulley 2008; Mohebtash 2009; Sabbatini 2007; Tsuda 2004). Antibodies were usually administered intravenously (11 out of 18). For other vaccine types, subcutaneous injections were most common (13 out of 18).

Concurrent treatment with immunomodulatory drugs was not allowed in 8 out of 36 studies. In an additional 11 studies, concomitant immunomodulatory agents were not part of the studied intervention, but no explicit statements were made about prohibition of such drugs in the protocol. In ten studies immunomodulatory drugs were part of the protocol (i.e. carboplatin-paclitaxel, cyclophosphamide, IL-2 +/- GM-CSF, or diphenhydramine) and one study allowed interruption of immunotherapy by chemotherapy for progressive disease (Reinartz 2004). Furthermore, two retrospective studies explicitly mentioned concurrent chemotherapy (Möbus 2003; Wagner 1993).

Outcomes

Information on immunological responses, clinical responses, survival and adverse events was available for 34, 21, 25 and 28 studies respectively.

Excluded studies

A summary of the excluded studies is given in the table of Characteristics of excluded studies. Frequent reasons for exclusion were inclusion of too few ovarian cancer patients and the impossibility to distinguish results of ovarian cancer patients from other patients.

Risk of bias in included studies

The assessment of risk of bias by means of the Delphi list was hindered by the fact that for five of the nine RCTs only meeting abstracts were available (Table 3). The four trials for which full texts were retrieved also did not report on some items of the Delphi list. Overall this resulted a median of four unreported items (one to five) per study. With this substantial lack of information, it is difficult to make any statement about biases in and validity of the randomised trials.

An overview of the assessment of study report quality and risk of biases of the non-randomised studies is provided in Table 4. Important observations from this table are the lack of clearly defined in-/exclusion criteria in 8 out of 27 studies combined with the serious under-reporting of baseline characteristics (16 out of 27 studies) which makes it impossible to evaluate whether the study populations were representative of the true population. Although the

investigational interventions were well described in the majority of studies (24 out of 27), information on the allowance or application of concomitant immunomodulatory treatment was frequently absent (18 out of 27). Albeit a clear description of outcome measures was available for 17 studies, an adequate calculation of sample size based on a clearly defined primary outcome measure was available for only two studies. Furthermore, the applied checklist shows that the justification of withdrawals and exclusions during the study as well as the presentation of study results are items that require serious attention in the reports of these non-randomised studies. Based on the above, the risk of bias in the studies included in this systematic review cannot be neglected. Especially selection bias (selection of a treatment population not comparable to control group or true population), attrition bias (inadequate reporting of withdrawal and exclusions during the study resulting in possible over- or underestimation of effect) and selective reporting bias are likely to affect the studies included in this review. The effects of interventions described below must therefore be interpreted with prudence.

Effects of interventions

Primary outcomes

Clinical efficacy

Tumor responses

Clinical responses to therapy were evaluated in 21 studies (Table 5). In the reports on these studies, criteria for evaluation and/or explicit description of tumour responses per patient as well as the time point at which the evaluation took place were frequently not available. For studies that did mention evaluation of tumour responses, response outcomes were based on either CA-125 levels combined with tumour imaging (Chianese-Bullock 2008; Diefenbach 2008; Ehlen 2005; Gordon 2004; Gulley 2008; Leffers 2009a; Sabbatini 2006; Ströhlein 2009; Tsuda 2004; van Zanten-Przybysz 2002), CA-125 alone (Nicholson 2004; Wagner 1993) or imaging alone (Odunsi 2007; Reinartz 2004). Only two studies explicitly mentioned evaluation of imaging according to the internationally accepted WHO or RECIST criteria (Leffers 2009a; Reinartz 2004; Tsuda 2004) and only two studies evaluated CA-125 levels according to GCIG criteria or described CA-125 levels in such a way that evaluation according to these criteria was possible for at least some patients (Leffers 2009a; van Zanten-Przybysz 2002). Strikingly, five studies stated that evaluation of tumour responses was performed, but results could not be found in the publications (Diefenbach 2008; Gulley 2008; Method 2002; Reinartz 2004; Wagner 1993). Complete or partial tumour responses in patients with evidence of disease at study entry were reported by only two studies (Gordon 2004; Odunsi 2007) in a small fraction of patients (3 out of 15 and 1 out of 18 respectively). These results need to be interpreted with caution as criteria for response evaluation were not defined.

Responses to 'secondary' treatment after immunotherapy

Although studies generally have a period of follow-up to obtain information on survival, in the majority of studies no report is given of subsequent treatment with and response to secondary chemotherapy. Seven studies mention that patients were treated with chemotherapy after immunotherapy (Berek 2004; Gordon 2004; Möbus 2003; Odunsi 2007; Reinartz 2004; Ströhlein 2009; van Zanten-Przybysz 2002), but only two studies, both investigating a monoclonal antibody targeting CA-125, report response to secondary chemotherapy in relation to immunological responses to immunotherapy (Gordon 2004; Reinartz 2004). In a preliminary report clinical responses of 28 out of 42 patients treated with chemotherapy for clinically relevant progression during or after antibody therapy were reported in conjunction with the induction of human-anti-mouse and anti-anti-idiotype antibodies. Although both patients with a complete response had strong humoral responses, similar or stronger antibody responses were also observed for patients with stable or progressive disease (Reinartz 2004). In the other study, shortly after monotherapy with a monoclonal antibody, 13 out of 20 patients received chemotherapy combined with the monoclonal antibody. In this study, clinical responses to chemo-immunotherapy, were only observed in patients with cellular responses to CA-125 and/or autologous tumour (Gordon 2004).

Survival

Definitions of survival used in the different studies varied greatly (Table 6 and Table 7). Furthermore, reliable statements about survival (dis)advantages can only be made based on RCTs. Only three studies were designed to primarily evaluate survival, however, no statistically significant differences in time to relapse and/or overall survival (OS) were found between patients treated with a monoclonal antibody or placebo (Berek 2001; Berek 2004; Berek 2009). Many non-RCTs have also evaluated survival, frequently by comparing survival of patients with robust immunological responses to patients with no or weak immunological responses to treatment (Table 6 and Table 7). These results should be interpreted with great caution as shorter survival in non-responders could merely be a reflection of the general condition of these patients and well-known clinical and pathological prognostic parameters.

Antigen-specific immunogenicity

Humoral responses

Monoclonal antibodies may induce anti-idiotype antibodies (Ab2), directed primarily against the administered monoclonal antibody, as well as anti-anti-idiotype antibodies (Ab3) directed towards the target antigen. Anti-idiotype and anti-anti-idiotype antibodies were evaluated in 10 and 9 out of 18 studies respectively (Table 8 and Table 9). Response percentages greatly varied (Ab2: 3 to 100%, Ab3: 0 to100%).

Eight studies (10 out of 18) of other vaccine types evaluated the induction of antigen-specific antibodies by ELISA, however only two studies clearly defined when an antibody titre or concentration was considered positive (Table 10) (Diefenbach 2008; Sandmaier 1999). Large differences in percentages of patients with measurable antigen-specific antibodies (IgG: 0 to 96%) existed. Possible explanations for these broad ranges are differences in 1) response definition, 2) number of treatment cycles after which humoral responses were measured and 3) targeted antigen.

Cellular responses

The induction of T-cells against the target antigen was investigated in 11 out of 18 monoclonal antibody studies (Table 11). The presence of antigen-specific T-cells was evaluated by commonly used tests, such as IFN-γ ELISPOT (Ehlen 2005; Gordon 2004; Method 2002; Sabbatini 2006), proliferation assay (Ma 2002; Noujaim 2001; van Zanten-Przybysz 2002), cytokine profiling (Noujaim 2001; Pfisterer 2006) and IFN-γ secretion assay (Ströhlein 2009). One study used the leukocyte migration inhibition assay (Wagner 1993), which nowadays is rarely used. As described above for humoral responses, response definitions were frequently lacking or inadequate. Nevertheless, cellular immunity against CA-125 was reported for 21 to 80% of patients. Antibody treatment targeting the membrane folate receptor however did not induce cellular responses (van Zanten-Przybysz 2002). Recognition of autologous tumour cells by induced T-cells was determined in two studies only, with positive responses in 5 out of 8 and 1 out of 2 patients respectively (Gordon 2004; Ströhlein 2009).

Antigen-specific cellular immune responses were evaluated for 12 out of 18 studies using other vaccine types (Table 12). The most frequently used assay was the IFN-γ ELISPOT assay, which was sometimes used to separately analyse $CD4^+$ and/or $CD8^+$ cells. Again response definitions for positive and/or vaccine-induced responses were frequently absent or unclear (8 out of 18). In four studies NY-ESO-1 specific T-cells were induced, with percentages of patients with NY-ESO-1-specific $CD8^+$ ranging from 33 to 67% (Diefenbach 2008; Odunsi 2007; Odunsi 2007a). After treatment with a vaccine targeting p53, p53-specific T-cells were observed in approximately 70% of patients, irrespective of whether short peptides or peptide-pulsed dendritic cells were used (Herrin 2007). Lastly, studies targeting multiple antigens demonstrated antigen-specific cellular immunity with varying immunogenicity of the different antigens targeted (Brossart 2000; Chianese-Bullock 2008; Chu 2008; Tsuda 2004).

Secondary outcomes

Carrier-specific immunogenicity

The majority of studies using a monoclonal antibody (17 out of 18) used a murine antibody and one study used a chimeric antibody construct (van Zanten-Przybysz 2002). Next to antigen-specific immunity, the induction of human-anti-mouse antibodies (HAMA) using HAMA-specific ELISA assays was assessed in 13 studies (Table 13). HAMA were present in 4 to 97% of patients immunized (Berek 2004; Braly 2009; Ehlen 2005; Gordon 2004; Method 2002; Möbus 2003; Pfisterer 2006; Reinartz 2004; Sabbatini 2006; Schultes 1998). It seems that the large variation between studies cannot be attributed to differences in dosage, but is best ascribed to different definitions of a HAMA response i.e. some studies only report robust responses, whereas others report all responses above a certain threshold. Furthermore, the point in time at which HAMA titers were measured is of importance as responses increase in frequency and strength with repeated administrations of the antibody (Gordon 2004; Method 2002; Möbus 2003).

Although six studies investigated synthetic carbohydrate antigens conjugated to the keyhole limpet haemocyanin (KLH) carrier protein (MacLean 1992; MacLean 1996; Sabbatini 2000; Sandmaier 1999; Sabbatini 2007), only one study reported on KLH-specific immunity (Sandmaier 1999). In this study, proliferative responses to stimulation with KLH and the KLH-antigen complex were substantially stronger than responses to the synthetic carbohydrate itself in all ovarian cancer patients tested, similar to what has previously been reported for viral vectors.

The use of vaccinia and fowlpox viruses as viral vectors was reported by three studies (Gulley 2008; Mohebtash 2009; Odunsi 2007a). Anti-vector immune responses were reported to be investigated by only one of these and occurred in all ovarian cancer patients treated (Gulley 2008).

Adverse events

For this review, adverse events were defined as any adverse change in health or side-effect that occurred in a person who participated in the clinical study while the patient was receiving the treatment, irrespective of whether the event could be attributed to the treatment received.

Although 28 studies mentioned adverse events, sufficiently detailed information on adverse events occurring during the study was available for only 21 out of 36 studies. Local adverse events were explicitly mentioned for 16 studies all of which used local administration of the vaccine (i.e. intradermal, intramuscular or subcutaneous injection). Although these studies report the presence of injection site reactions, 50% did not further specify the type of local adverse events witnessed. When local adverse events were further specified, these were best summarized as pain at the injection

site and local inflammatory responses (erythema, induration, pruritis). In one study 3 out of 30 patients developed a small abscesses and ulceration upon intradermal injection, after which the adjuvant was omitted from the vaccine for these patients (Freedman 1998).

Systemic adverse events occurred in 23 studies and were not observed in 2 studies. For the remaining 11 studies no information on systemic adverse events could be deduced from the manuscript. Autoimmunity was reported by two studies. In one study a patient with strong immunological responses to the vaccine developed a symptomatic hypothyroidism necessitating replacement therapy (Diefenbach 2008). A minor induction of anti-nuclear antibodies (grade I according to Common Terminology Criteria for Adverse Events (CTCAE) v3.0 (Trotti 2003)) was described for two patients receiving a multi-peptide vaccine (Chianese-Bullock 2008). Allergic reactions were described for a total of 14 patients (Berek 2009; Braly 2009; Ehlen 2005; MacLean 1992; Möbus 2003; Pfisterer 2006; Ströhlein 2009). Allergic reactions were mild and easily managed, e.g. hypersensitivity, allergic exanthema, and urticaria. When study treatment was continued, this did not result in renewed allergic reactions (Braly 2009; Ehlen 2005; Möbus 2003; Pfisterer 2006).

Other systemic adverse events reported, irrespective of whether attributable to the investigated drug, included hematologic changes (e.g. anaemia, leucopenia), flu-like symptoms (including fatigue, myalgia, arthralgia, headache, fever and chills) and gastrointestinal events (e.g. nausea, vomiting, diarrhoea, and abdominal pain), most of which were classified as grade I or II events. Grade III or IV adverse events were reported by eleven studies. For two studies it was however unclear whether the participating ovarian cancer patients experienced these events (Gulley 2008; Tsuda 2004) and in one study serious adverse events undoubtedly reflected progressive disease (Leffers 2009a). In the one study, which investigated p53-based immunization strategies combined with IL-2, grade III/IV adverse events were observed in 42% of patients in each arm of the study and ascribed to the IL-2 adjuvant, which was thereafter omitted from the regimen for these patients (Herrin 2007). Severe or life-threatening flu-like symptoms and gastro-intestinal events were observed in 7 to 30% of patients in 7 studies investigating monoclonal antibodies targeting CA-125 (Berek 2004; Berek 2009; Braly 2009; Ehlen 2005; Gordon 2004; Pfisterer 2006; Sabbatini 2006). However as no differences in serious adverse events were observed between patients treated with the monoclonal antibody and placebo controls, it is unlikely that these can be attributed to the monoclonal antibody treatment.

DISCUSSION

The aim of this review was to evaluate clinical and immunological efficacy of antigen-specific active immunotherapy in ovarian cancer, whilst also obtaining an impression of safety and tolerability of this treatment modality. The antigen-specific active immunotherapy described in this review can largely be divided into two strategies (1) the administration of antibodies targeting a specific tumour antigen and (2) the administration of or parts of a specific tumour antigen itself. As expected, most studies were non-RCTs.

Antigen-specific humoral and/or cellular immunogenicity of the different interventions showed great variation for both monoclonal antibody studies and studies using other strategies. This variation may at least be partially attributed to the variation in immunological response definitions used by the different studies. It is therefore not possible to reliably compare studies and infer which intervention and/or immunization strategy is most promising for the induction of strong anti-tumour immunity. Furthermore, only two studies evaluated recognition of autologous tumour cells in vitro and none evaluated immune responses at the tumour site. Although obtaining autologous tumour material may be burdensome, such assays would be extremely valuable as they comprise true interactions between induced immunity and tumour cells and could as such provide important information on how to continue improvement of immunotherapeutic strategies to reach clinical effectiveness.

Clinical responses to immunotherapy (i.e. tumour responses, responses to secondary treatment and survival benefits) were observed only incidentally and when described reliability of results was questionable due to the absence of clear response definitions. Furthermore, for studies in which a monoclonal antibody targeting CA-125 was used, the use of CA-125 as a marker for clinical response is questionable. An additional important comment regarding the likelihood of clinical responses to immunotherapy especially in uncontrolled studies which frequently include patients with recurrent disease, is the fact that this likelihood may be affected by the disease status at start of treatment (Leffers 2009). The indication for immunotherapeutic treatment in the adjuvant setting is supported by the observation of enhanced antigen-specific responses to immunotherapy when combined with chemotherapeutic agents currently or previously used in the primary treatment of ovarian cancer i.e. docetaxel or cyclophosphamide (Garnett 2008; Laheru 2008). Three large RCTs using a monoclonal CA-125 antibody in the adjuvant setting after successful primary therapy however did not demonstrate any differences in time to relapse and/or OS between the treatment and placebo arm (Berek 2001; Berek 2004;Berek 2009), which indicates that despite immunogenicity, CA-125 targeted monoclonal antibody therapy is clinically ineffective. For the studies of other vaccine types, no such conclusions can be made at this time as large RCTs and more studies in the adjuvant, rather than recurrent setting have yet to be performed for the different strategies.

Adverse events, reported in sufficient detail for interpretation, were reported in 60% of studies. A distinction was made between lo-

cal and systemic events. The latter were further subdivided in autoimmunity, allergy and other adverse events. We did not evaluate whether adverse events could be or were considered attributable to the treatment studied, although for local adverse events this is indisputably the case. Inflammatory reactions and pain at the injection site were frequently reported for studies using intradermal, subcutaneous or intramuscular application. Severe or life-threatening systemic adverse events were reported by 11 studies, 7 of which investigated monoclonal antibodies targeting CA-125. For these monoclonal antibody studies, no pattern suggestive of a underlying treatment-associated process could be identified and events were often considered to be associated with ovarian cancer progression. Serious adverse events in another study were considered to be related to IL-2 given as an adjuvant to the antigen-specific active immunization.

A disturbing observation regarding adverse events is the lack of uniformity in adverse event reporting. Reporting of safety and tolerability of new treatment strategies should have high priority in all studies of investigational drugs, especially in uncontrolled phase I and II studies. To promote uniformity in adverse event evaluation and reporting as well as the comparability of adverse events between studies, in addition to the NCI CTCAE (Trotti 2003), the Brighton Collaboration (Brighton Collaboration 2009) has committed itself to develop standardized, widely disseminated and globally accepted case definitions for an exhaustive number of adverse events following immunisation as well as guidelines for data collection, analysis, and presentation. These case-definitions and guidelines are freely available and we strongly recommend that, where applicable, these are used for all immunotherapeutic studies.

Interestingly, for six studies described in this review, information from the study was collected from a meeting abstract only and often this meeting abstract was several years old. The lack of full text manuscripts, even after contacting abstract authors, strongly suggests the existence of a publication bias. To avoid the disappearance of negative studies, registration of trials in a prospective trial register is widely recommended and supported by the International Committee of Medical Journal Editors (ICMJE). However, initially in 2005 registration was only requested for RCTs. Since July 1, 2008 all trials prospectively assigning human participants to one or more health-related interventions to evaluate the effects on health outcomes are required to register in a clinical trial register approved by the WHO. From the ongoing studies section it is however apparent that despite registration in a prospective trial register, studies may suffer from publication bias as several relatively small studies started more than five years ago have not yet been published to date or closed according to the trial register. In addition to registration in trial registers, the uniform requirements for manuscripts submitted to biomedical journals drafted by the ICMJE encourage uniformity in reporting of clinical trials by stating ethical principles in conduct and reporting of research as well as proving recommendations relating to specific elements of editing and writing. As is obvious from this review, the scientific community might benefit substantially if also early phase uncontrolled clinically trials would strive for uniformity in trial conduct and reporting.

This review also emphasizes another aspect of immunotherapeutic studies that warrants serious attention in the immunotherapeutic scientific community i.e. the lack of consensus on 1) what assays to use to establish immunogenicity of an intervention (Britten 2008), 2) what cut-offs to use to define true immunological responses and 3) response definitions for clinical efficacy. Given these large inconsistencies it is evident that the elucidation of what type of immunological response is necessary for and/or a surrogate marker of clinical activity of an immunotherapeutic intervention is burdensome.

In summary, this review describes 36 immunotherapy studies in ovarian cancer patients. The most striking observations of this review unfortunately do not concern the aim of the review, but address the lack of uniformity in conduct and reporting of early phase immunotherapy studies. When temporarily discarding this methodological heterogeneity, it seems that although all strategies described are capable of inducing immunological responses, be it humoral or cellular, clinically effectiveness has thus far not been convincingly demonstrated. The largest body of evidence is available for CA-125 directed antibody therapy, which has been studied in 1505 patients participating in 15 studies. As complete or partial clinical responses were reported in only one study and three large RCTs did not demonstrate any clinical benefit of antibody treatment, we feel that it is unlikely that clinical effectiveness of CA-125 directed antibody therapy for ovarian cancer will ever be obtained. However, in view of the immunological responses to and the usually mild side-effects, we feel that further investigation of other antigen-specific active immunotherapy strategies in ovarian cancer is worthwhile.

AUTHORS' CONCLUSIONS

Implications for practice

At this point in time, there is no evidence of effective immunotherapy for ovarian cancer. Although promising immunological responses have been observed for most strategies evaluated, these do not coincide with clinical benefits for ovarian cancer patients. Furthermore, there are currently no immunological surrogate markers that correlate with clinical outcomes. Until evidence of true clinical effectiveness is available, immunotherapy should therefore not be offered as an alternative to standard therapy for primary or recurrent ovarian cancer.

Implications for research

Our primary recommendation relates to the necessity of unifor-

mity in trial conduct and reporting. Not until universally accepted immunological and clinical response definitions and guidelines for adverse events reporting are adopted in immunotherapeutic studies, will it be possible to make any inferences about the achievability of immunotherapy as a treatment for ovarian cancer. Furthermore, expanding evaluation of immunogenicity to include recognition of autologous tumour is advisable. Given the usually mild side-effects and the immunological responses witnessed in most studies, we feel that further investigation of antigen-specific active immunotherapy other than CA-125 targeted antibody therapy in ovarian cancer in RCTs is worthwhile.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Berek 2001

Methods	Randomized placebo controlled trial
Participants	252 stage III/IV ovarian cancer patients after successful primary surgery and chemotherapy
Interventions	Intravenous monoclonal antibody (oregovomab - CA125) versus Intra. placebo
Outcomes	Survival (time to relapse) Immune responses: humoral (Ab2, HAMA)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	method of randomisation not described, only abstract available
Allocation concealment?	Unclear risk	method of randomisation not described, only abstract available
Blinding? All outcomes	Low risk	double blind study

Berek 2004

Methods	Randomized placebo controlled phase II Trial
Participants	145 stage III/IV ovarian cancer patients with complete clinical response to primary therapy
Interventions	Intravenous monoclonal antibody (oregovomab) versus Intra. placebo
Outcomes	Survival (time to relapse / overall survival) Immune Responses: humoral (Ab2, HAMA) Adverse Events
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	method of randomisation not described

Berek 2004 (*Continued*)

Allocation concealment?	Unclear risk	not described
Blinding? All outcomes	Unclear risk	not described

Berek 2009

Methods	Randomized placebo controlled phase III trial
Participants	371 stage III/IV ovarian cancer patients with complete clinical response to primary therapy
Interventions	Intravenous monoclonal antibody (oregovomab) versus Intra. placebo
Outcomes	Survival (time to relapse) Immune responses Adverse events
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	not described
Allocation concealment?	Low risk	centralized randomisation procedure
Blinding? All outcomes	Low risk	patients, physicians and sponsor were all blinded to treatment assignment and post-randomisation immune response and CA-125 measurements

Braly 2009

Methods	Randomized Controlled phase II Trial
Participants	40 stage III/IV ovarian cancer patients after primary debulking surgery with or without residual disease
Interventions	Intravenous monoclonal antibody (oregovomab - CA125): concurrent (SIM) or delayed (OWD) with standard carboplatin/paclitaxel primary chemotherapy
Outcomes	Survival (progression free survival) Clinical Responses Immune Responses Adverse Events
Notes	

Braly 2009 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Low risk	block randomisation
Allocation concealment?	Unclear risk	not described
Blinding? All outcomes	High risk	patient and physician not blinded to treatment allocation; blinding of outcome assessor not described

Brossart 2000

Methods	Uncontrolled phase I/II study
Participants	10 patients with measurable residual or recurrent breast or ovarian cancer (3 ovarian cancer patients)
Interventions	Subcutaneous peptide pulsed Dendritic Cells (n = 1: Her-2/Neu; n = 2 MUC-1)
Outcomes	Tumor Responses Immune Response Adverse Events
Notes	

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	High risk	uncontrolled trial
Allocation concealment?	High risk	uncontrolled trial
Blinding? All outcomes	High risk	uncontrolled trial

Chianese-Bullock 2008

Methods	Uncontrolled phase I study
Participants	9 ovarian cancer patients with or without residual or recurrent disease after primary therapy
Interventions	Subcutaneous & intradermal multi peptide vaccine (FBP, Her-2/Neu & MAGE-A1) Adjuvant: Montanide ISA-51, GM-CSF

Chianese-Bullock 2008 (*Continued*)

Outcomes	Tumor Responses Immune Response Adverse Events
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	High risk	uncontrolled trial
Allocation concealment?	High risk	uncontrolled trial
Blinding? All outcomes	High risk	uncontrolled trial

Chu 2008

Methods	Randomized Controlled phase I/II study
Participants	14 ovarian cancer patients with complete clinical response to primary therapy (10 received treatment so far)
Interventions	Intradermal peptide pulsed Dendritic Cells (Her-2/Neu, hTERT, PADRE): vaccine alone versus single dose of cyclophosphamide prior to first vaccination
Outcomes	Tumor Responses Immune Response Adverse Events
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	method of randomisation not described, only abstract available
Allocation concealment?	Unclear risk	method of randomisation not described, only abstract available
Blinding? All outcomes	High risk	patient and physician not blinded to treatment allocation; blinding of outcome assessor not described

Diefenbach 2008

Methods	Uncontrolled phase I study
Participants	9 ovarian cancer patients with complete clinical response to primary therapy
Interventions	Subcutaneous short peptide (NY-ESO-1) Adjuvant: Montanide ISA-51
Outcomes	Survival (time to progression) Tumor Responses Immune Responses: cellular and humoral Adverse Events
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	High risk	uncontrolled trial
Allocation concealment?	High risk	uncontrolled trial
Blinding? All outcomes	High risk	uncontrolled trial

Ehlen 2005

Methods	Uncontrolled phase II study
Participants	13 ovarian cancer patients with measurable recurrent disease
Interventions	Intravenous monoclonal antibody (oregovomab - CA125)
Outcomes	Survival (time to progression / survival) Tumor Responses Immune Responses: humoral (Ab2, Ab3, HAMA), cellular Adverse Events
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	High risk	uncontrolled trial
Allocation concealment?	High risk	uncontrolled trial

Ehlen 2005 (*Continued*)

Blinding? All outcomes	High risk	uncontrolled trial

Freedman 1998

Methods	Randomized Controlled phase II study
Participants	30 ovarian cancer patients previously treated with platinum-based chemotherapy (disease status at study entry not described)
Interventions	Subcutaneous KLH conjugate (Sialyl-Tn) at two different dosages Adjuvant: detox B
Outcomes	Survival (progression free interval / survival) Tumor Responses Adverse Events
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	method of randomisation not described, only abstract available
Allocation concealment?	Unclear risk	method of randomisation not described, only abstract available
Blinding? All outcomes	Low risk	double blind study

Gordon 2004

Methods	Uncontrolled phase II study
Participants	20 ovarian cancer patients with recurrent disease
Interventions	Intravenous monoclonal antibody (oregovomab - CA125)
Outcomes	Survival (time to progression / survival) Tumor Responses Immune Responses: humoral (Ab2, Ab3, HAMA), cellular Adverse Events
Notes	

Gordon 2004 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	High risk	uncontrolled trial
Allocation concealment?	High risk	uncontrolled trial
Blinding? All outcomes	High risk	uncontrolled trial

Gulley 2008

Methods	Uncontrolled phase I/II study
Participants	25 patients with CEA or MUC1 over-expressing metastatic cancer with progressive disease following standard chemotherapy (ovarian cancer n = 3)
Interventions	Subcutaneous recombinant pox virus (CEA, MUC1): 1x vaccinia, ≥4 fowlpox Adjuvant: local GM-CSF
Outcomes	Survival (progression free survival / overall survival) Immune Responses: cellular, humoral Adverse Events
Notes	

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	High risk	uncontrolled trial
Allocation concealment?	High risk	uncontrolled trial
Blinding? All outcomes	High risk	uncontrolled trial

Herrin 2007

Methods	Randomized Controlled phase II study
Participants	21 stage III/IV or recurrent ovarian cancer patients with no evidence of disease
Interventions	Subcutaneous short peptide versus intravenous peptide pulsed Dendritic Cells (p53) Adjuvant: Montanide ISA-51 + GM-CSF + IL-2 (peptide) vs IL-2 (dendritic cells)

Herrin 2007 (*Continued*)

Outcomes	Survival (progression free survival / overall survival) Tumor Responses Immune Responses: cellular Adverse Events
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	method of randomisation not described, only abstract available
Allocation concealment?	Unclear risk	method of randomisation not described, only abstract available
Blinding? All outcomes	High risk	patient and physician not blinded to treatment allocation; blinding of outcome assessor not described

Leffers 2009a

Methods	Uncontrolled phase II study
Participants	20 epithelial ovarian cancer patients with (biochemical) recurrence not (yet) eligible for renewed chemotherapy
Interventions	Subcutaneous synthetic long peptides (p53) Adjuvant: Montanide ISA51
Outcomes	Tumor Responses Immune Responses: humoral, cellular Adverse events
Notes	

Ma 2002

Methods	Uncontrolled study
Participants	4 ovarian cancer patients (disease status at study entry not described)
Interventions	monoclonal antibody (MJ01- CA125)
Outcomes	Immune Response: cellular
Notes	

Ma 2002 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	High risk	uncontrolled trial
Allocation concealment?	High risk	uncontrolled trial
Blinding? All outcomes	High risk	uncontrolled trial

MacLean 1992

Methods	Uncontrolled phase I study
Participants	10 ovarian cancer patients with residual or recurrent disease
Interventions	Subcutaneous KLH conjugate (Thomson Friedenreich) Adjuvant: detox B
Outcomes	Tumor Responses Immune Responses: humoral Adverse Events
Notes	

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	High risk	uncontrolled trial
Allocation concealment?	High risk	uncontrolled trial
Blinding? All outcomes	High risk	uncontrolled trial

MacLean 1996

Methods	Uncontrolled phase II study
Participants	34 ovarian cancer patients with evaluable residual or recurrent disease
Interventions	Subcutaneous KLH conjugate (Sialyl-Tn) Adjuvant: detox B

MacLean 1996 (*Continued*)

Outcomes	Survival (trial entry to death) Immune Response: humoral
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	High risk	uncontrolled trial
Allocation concealment?	High risk	uncontrolled trial
Blinding? All outcomes	High risk	uncontrolled trial

Method 2002

Methods	Randomized Controlled Study
Participants	102 ovarian cancer patients after primary therapy (disease status at study entry not described)
Interventions	Intravenous monoclonal antibody (oregovomab - CA125): 2 gifts versus 3 gifts, versus 6 gifts
Outcomes	Tumor Responses Immune Response: humoral (Ab2, HAMA), cellular Adverse Events
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	method of randomisation not described, only abstract available
Allocation concealment?	Unclear risk	method of randomisation not described, only abstract available
Blinding? All outcomes	High risk	patient and physician not blinded to treatment allocation; blinding of outcome assessor not described

Mohebtash 2009

Methods	Uncontrolled study
Participants	31 metastatic ovarian and breast cancer patients (ovarian cancer n = 17)
Interventions	Subcutaneous recombinant pox virus (MUC1 and CEA) adjuvant: local GM-CSF
Outcomes	Survival: median time to progression 2 months (range 1-36) Adverse Events: no severe adverse events, mostly locoregional grade 1 or 2 reactions
Notes	max. 3 patients overlap with Gulley 2008

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	High risk	uncontrolled trial
Allocation concealment?	High risk	uncontrolled trial
Blinding? All outcomes	High risk	uncontrolled trial

Möbus 2003

Methods	Retrospective uncontrolled study
Participants	44 ovarian cancer patients with clinical recurrence after primary therapy
Interventions	Intravenous monoclonal antibody (oregovomab - CA125)
Outcomes	Survival (time first dose to death / overall survival) Immune Response: humoral (Ab2, Ab3, HAMA) Adverse Events
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	High risk	uncontrolled trial
Allocation concealment?	High risk	uncontrolled trial
Blinding? All outcomes	High risk	uncontrolled trial

Nicholson 2004

Methods	Uncontrolled phase I study
Participants	26 epithelial ovarian cancer patients with residual disease (n = 19), microscopic disease (n = 3) after chemotherapy or 2nd complete remission (n = 4)
Interventions	monoclonal antibody (HMFG1 - Muc1); first gift intraperitoneal (n = 16) or intravenous (n = 10) , then id boosts Adjuvant: aluminium hydroxide
Outcomes	Tumor Responses Immune Response: humoral (Ab2) Adverse Events
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	High risk	uncontrolled trial
Allocation concealment?	High risk	uncontrolled trial
Blinding? All outcomes	High risk	uncontrolled trial

Nishikawa 2006

Methods	Uncontrolled phase II study
Participants	4 epithelial ovarian cancer patients after primary debulking surgery (disease status at study entry not described)
Interventions	short peptide (NY-ESO-1) Adjuvant: incomplete Freund's adjuvant
Outcomes	Immune Responses: cellular
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	High risk	uncontrolled trial
Allocation concealment?	High risk	uncontrolled trial

Blinding? All outcomes	High risk	uncontrolled trial

Noujaim 2001

Methods	Retrospective uncontrolled study
Participants	184 ovarian cancer patients with clinically or radiologically suspected recurrence
Interventions	Intravenous monoclonal antibody (oregovomab - CA125)
Outcomes	Survival (overall survival) Immune Responses: humoral (Ab3), cellular
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	High risk	uncontrolled trial
Allocation concealment?	High risk	uncontrolled trial
Blinding? All outcomes	High risk	uncontrolled trial

Odunsi 2007

Methods	Uncontrolled phase I study
Participants	18 ovarian cancer patients after chemotherapy for primary or recurrent disease with or without residual disease
Interventions	Subcutaneous short peptide (NY-ESO-1) Adjuvant: incomplete Freund's adjuvant
Outcomes	Survival: median time to progression 19.0 months Tumor Responses: 1x CR, 17x unknownnown Immune Responses: humoral, cellular Adverse Events: well-tolerated, no further description
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Adequate sequence generation?	High risk	uncontrolled trial
Allocation concealment?	High risk	uncontrolled trial
Blinding? All outcomes	High risk	uncontrolled trial

Odunsi 2007a

Methods	Uncontrolled phase I/II study
Participants	19 ovarian cancer patients without evidence of disease after primary therapy
Interventions	intradermal recombinant virus (NY-ESO-1); 1x vaccinia virus, 6x fowlpox boost
Outcomes	Survival (disease free survival) Immune Responses: humoral, cellular Adverse Events
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	High risk	uncontrolled trial
Allocation concealment?	High risk	uncontrolled trial
Blinding? All outcomes	High risk	uncontrolled trial

Pfisterer 2006

Methods	Uncontrolled phase I study
Participants	36 Stage I-IV ovarian cancer patients within 6 weeks after completion of chemotherapy for recurrent disease (disease status at study entry not described)
Interventions	Subcutaneous monoclonal antibody (abagovomab - CA125)
Outcomes	Immune Responses: humoral (Ab3, HAMA), cellular Adverse Events
Notes	

Risk of bias

Pfisterer 2006 (*Continued*)

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	High risk	uncontrolled trial
Allocation concealment?	High risk	uncontrolled trial
Blinding? All outcomes	High risk	uncontrolled trial

Reinartz 2004

Methods	Uncontrolled multicenter phase Ib/II study
Participants	119 patients with ovarian cancer after at least primary treatment (disease status at entry not described)
Interventions	Intramuscular monoclonal antibody (ACA125 - CA125)
Outcomes	Survival (time first dose to death) Tumor Responses Adverse Events
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	High risk	uncontrolled trial
Allocation concealment?	High risk	uncontrolled trial
Blinding? All outcomes	High risk	uncontrolled trial

Sabbatini 2000

Methods	Uncontrolled phase I study
Participants	25 ovarian cancer patients with complete clinical response to chemotherapy after residual or recurrent disease following primary therapy
Interventions	Subcutaneous KLH conjugate (LewisY penta saccharide - MUC-1) Adjuvant: QS-21

Sabbatini 2000 (*Continued*)

Outcomes	Survival (time to progression) Immune Responses: humoral Adverse Events
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	High risk	uncontrolled trial
Allocation concealment?	High risk	uncontrolled trial
Blinding? All outcomes	High risk	uncontrolled trial

Sabbatini 2006

Methods	Randomized, open-label multicenter phase I study
Participants	42 stage II-IV ovarian cancer patients after chemotherapy for recurrence of disease with complete clinical response or measurable disease (<2 cm)
Interventions	Intramuscular (i.m.) or subcutaneous (s.c.) monoclonal antibody (abagovomab - CA125): 4 cohorts (2x i.m.; 2x s.c.; 0.2mg or 2mg)
Outcomes	Survival (time to progression) Tumor Responses Immune Response: humoral (Ab3, HAMA), cellular Adverse Events
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	standard 2x2 factorial design
Allocation concealment?	Unclear risk	not described
Blinding? All outcomes	Unclear risk	patient and physician not blinded to treatment allocation; blinding of outcome assessor not described

Sabbatini 2007

Methods	Uncontrolled phase I/II study
Participants	11 epithelial ovarian cancer patients with complete clinical remission after primary therapy or chemotherapy for recurrent disease
Interventions	subcutanous heptavalent KLH conjugate (GM2, Globo-H, Lewis Y, Tn-MUC1, Tn(c) sTN(c), TF(c))
Outcomes	Survival (time to treatment failure) Immune responses: humoral
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	High risk	uncontrolled trial
Allocation concealment?	High risk	uncontrolled trial
Blinding? All outcomes	High risk	uncontrolled trial

Sandmaier 1999

Methods	Uncontrolled phase II study
Participants	40 breast or ovarian cancer (n = 7) patients who underwent high-dose chemotherapy and autologous or syngeic stem cell rescue (disease status at study entry unknown)
Interventions	subcutanous KLH conjugate (Sialyl-Tn) Adjuvant: detox B
Outcomes	Immune Responses: humoral, cellular
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	High risk	uncontrolled trial
Allocation concealment?	High risk	uncontrolled trial

Sandmaier 1999 (*Continued*)

Blinding? All outcomes	High risk	uncontrolled trial

Schultes 1998

Methods	Retrospective Uncontrolled study
Participants	75 stage I-IV ovarian cancer patients (disease status at study entry not described)
Interventions	Intravenous monoclonal antibody (oregovomab - CA125)
Outcomes	Survival (overall survival) Immune Responses: humoral (Ab2, Ab3, HAMA)
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	High risk	uncontrolled trial
Allocation concealment?	High risk	uncontrolled trial
Blinding? All outcomes	High risk	uncontrolled trial

Ströhlein 2009

Methods	Uncontrolled phase I study
Participants	9 patients with progressive peritoneal carcinomatosis (ovarian cancer n = 2)
Interventions	Intraperitoneal trifunctional antibody targeting EpCAM (n = 1) or Her2/Neu (n = 1)
Outcomes	Survival: not reported separately for ovarian cancer patients Tumor Responses Immune Responses: cellular, humoral (HAMA) Adverse Events
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	High risk	uncontrolled trial

Ströhlein 2009 (*Continued*)

Allocation concealment?	High risk	uncontrolled trial
Blinding? All outcomes	High risk	uncontrolled trial

Tsuda 2004

Methods	Uncontrolled phase I/II study
Participants	14 patients with gynaecological cancer after primary therapy (ovarian cancer n = 5; NED n = 2)
Interventions	Subcutaneous individualised short peptide cocktail Adjuvant: Montanide ISA-51
Outcomes	Tumor Responses Immune Responses: humoral, cellular Adverse Events: not separately described for ovarian cancer patients
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	High risk	uncontrolled trial
Allocation concealment?	High risk	uncontrolled trial
Blinding? All outcomes	High risk	uncontrolled trial

van Zanten-Przybysz 2002

Methods	Uncontrolled phase I/II study
Participants	5 patients with residual or recurrent ovarian cancer after primary debulking surgery and at least one course of chemotherapy
Interventions	Intravenous monoclonal antibody (c-MOv18 - membrane folate receptor)
Outcomes	Survival: median time first dose to death 22.0 months Tumor Responses: 3x PD, 2x SD Immune Responses: cellular Adverse Events: max. grade I events
Notes	

van Zanten-Przybysz 2002 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	High risk	uncontrolled trial
Allocation concealment?	High risk	uncontrolled trial
Blinding? All outcomes	High risk	uncontrolled trial

Wagner 1993

Methods	Retrospective Uncontrolled study
Participants	58 patients with advanced stage ovarian cancer after primary treatment with high pre-operative CA-125 levels (disease status at study entry not described)
Interventions	Intravenous monoclonal antibody fragments ($F(Ab)_2$-fragements of MAb OC125 - CA125)
Outcomes	Survival Tumor Responses Immune Responses: humoral (Ab2), cellular
Notes	

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	High risk	uncontrolled trial
Allocation concealment?	High risk	uncontrolled trial
Blinding? All outcomes	High risk	uncontrolled trial

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Anderson 2000	only one EOC patient; no AASI
Bender 2007	only one EOC patient
Carbone 2005	only one EOC patient
Disis 1999	impossible to distinguish between other and ovarian cancer patients
Disis 2000	impossible to distinguish between other and ovarian cancer patients
Disis 2002	impossible to distinguish between other and ovarian cancer patients
Disis 2002a	only one EOC patient
Disis 2004	impossible to distinguish between other and ovarian cancer patients
Disis 2004a	only one EOC patient
Hernando 2002	autologous tumour lysate vaccine
Hernando 2007	only one EOC patient
Holmberg 2000	impossible to distinguish between breast & ovarian cancer patients
Hui 1997	no AASI
Jager 2006	only one EOC patient
Knutson 2001	only one EOC patient
Knutson 2002	EOC patients withdrew before evaluation of immune responses
Letsch 2008	impossible to distinguish between other and ovarian cancer patients
Loveland 2006	only one EOC patient
Marshall 2005	only one ovarian cancer patient
Miotti 1999	autologous T-cell vaccine
Morse 1999	impossible to distinguish between other and ovarian cancer patients
Morse 2003	uncertain if and how many ovarian cancer patients were included
Murray 2002	only one EOC patient

(*Continued*)

Parkhurst 2004	no EOC patients
Reddish 1996	impossible to distinguish between other and ovarian cancer patients
Salazar 2006	impossible to distinguish between other and ovarian cancer patients
Schiffman 2002	no immunizations carries out
Yacyshyn 1995	additional results to MacLean 1992; irrelevant for review
Zaks 1998	impossible to distinguish between other and ovarian cancer patients

Characteristics of ongoing studies *[ordered by study ID]*

NCT00017537

Trial name or title	phase IB Trial of Active Specific Immunotherapy With MVF-HER-2(628-647) and CRL1005 Copolymer Adjuvant in Patients With Metastatic Cancer
Methods	Uncontrolled phase Ib study
Participants	5-25 Histologically confirmed metastatic and/or recurrent solid tumour, especially the following: Breast, Ovarian, Non-small cell lung cancer, and Gastric adenocarcinoma patients
Interventions	i.m. MVF-HER-2(628-647)-CRL 1005 vaccine
Outcomes	optimum biologic dose toxicity clinical responses
Starting date	March 2000
Contact information	
Notes	

NCT00019084

Trial name or title	Vaccine therapy with tumour specific mutated p53 or ras peptides alone or in combination with cellular immunotherapy with peptide activated lymphocytes (PAL cells) along with subcutaneous IL-2
Methods	Phase II study
Participants	max. 70 patients with incurable advanced cancer expressing mutant p53 or ras

NCT00019084 (*Continued*)

Interventions	patient-specific mutant p53 or ras peptide pulsed antigen-presenting cells plus GM-CSF, or patient-specific mutant p53 or ras peptide pulsed antigen-presenting cells plus peptide-activated lymphocytes and IL-2
Outcomes	Immune responses Clinical responses
Starting date	February 1996
Contact information	
Notes	Completion date not mentioned. No published records available

NCT00019916

Trial name or title	Vaccine Therapy With Tumor Specific p53 Peptides in Adult Patients With Adenocarcinoma of the Breast or Ovary
Methods	Randomized phase I/II study
Participants	max. 34 patients with adenocarcinoma of breast or ovary without therapeutic options
Interventions	s.c. p53 peptide vaccine, or i.v. p53 peptide vaccine
Outcomes	Immune responses Safety Clinical responses
Starting date	June 2000
Contact information	
Notes	Completion date not mentioned. No published records available

NCT00023634

Trial name or title	An Early Phase Study of an EGFRvIII Peptide Based Vaccine in Patients With EGFRvIII Expressing Cancers
Methods	Phase I study
Participants	24 patients with gastric, ovarian or prostate cancer or anaplastic astrocytoma (ovarian cancer patients in first complete remission)
Interventions	s.c. EGFRvIII peptide admixed with GM-CSF, or i.d. EGFRvIII peptide admixed with keyhole limpet hemocyanin

NCT00023634 (*Continued*)

Outcomes	toxicity immune responses
Starting date	June 2001
Contact information	
Notes	

NCT00034138

Trial name or title	A Comparative Pharmacokinetics and Safety Study of OvaRex MAb-B43.13 in Patients With Ovarian Epithelial Carcinoma
Methods	Randomized phase I/II study
Participants	24 stage III/IV ovarian cancer after primary therapy
Interventions	OvaRex MAb-B43.13 ascites fluid product and/or OvaRex MAb-B43.13 cell culture product
Outcomes	Safety Survival
Starting date	March 2002
Contact information	
Notes	Study completion December 2007. No published records available

NCT00034372

Trial name or title	Multicenter Clinical Trial of Intravenous OvaRex MAb-B43.13 as Post-Chemotherapy Consolidation for Ovarian Carcinoma
Methods	Phase II
Participants	102 ovarian cancer patients with complete clinical response to primary treatment
Interventions	i.v. OvaRex MAb-B43 i.v.
Outcomes	Survival Immune responses
Starting date	September 2000
Contact information	

NCT00034372 (*Continued*)

Notes	Study completion December 2007. No published records available

NCT00091000

Trial name or title	An Open Label Pilot Study to Evaluate the Safety and Tolerability of PANVAC-V (Vaccinia) and PANVAC-F (Fowlpox) in Combination With Sargramostim in Adults With Metastatic Carcinoma
Methods	Phase II
Participants	51 patients with histologically confirmed colorectal, non-colorectal, ovarian, or breast carcinoma with evidence of disease
Interventions	s.c. recombinant vaccinia-CEA-MUC-1-TRICOM vaccine subcutaneously (prime), and s.c. recombinant fowlpox-CEA-MUC-1-TRICOM vaccine (boost) adjuvant: s.c. GM-CSF
Outcomes	safety clinical responses immune responses
Starting date	July 2004
Contact information	
Notes	

NCT00373217

Trial name or title	Evaluation of the Immunogenicity of Vaccination With Synthetic Peptides in Adjuvant in Patients With Advanced Ovarian, Primary Peritoneal, or Fallopian Tube Cancer
Methods	Phase II study
Participants	28 primary stage III/IV ovarian cancer patients
Interventions	neoadjuvant paclitaxel/carboplatin followed by surgical debulking, vaccine therapy*, adjuvant paclitaxel/carboplatin or, surgical debulking, vaccine therapy*, followed by adjuvant paclitaxel/carboplatin *i.d. & s.c. synthetic peptides, (MAGE-A1:161-169, FBP:1901-199, Her-2/neu:369-377, MAGE-A1:96-104, and Her-2/neu:754-762) and tetanus toxoid helper peptide adjuvant: Montanide ISA-51
Outcomes	Immune responses
Starting date	April 2006
Contact information	

NCT00373217 (*Continued*)

Notes	

NCT00381173

Trial name or title	A Phase 1 Open-Label Study of the Safety and Feasibility of ZYC300 Administration With Cyclophosphamide Pre-Dosing
Methods	Phase I
Participants	22 advanced stage malignancies with evidence of disease and no therapeutic options
Interventions	i.m. ZYC300 (a plasmid DNA formulated within biodegradable microencapsulated particles) with i.v. cyclophosphamide
Outcomes	safety Immune Responses Tumor Responses
Starting date	November 2006
Contact information	
Notes	Study completion January 2009. No published records available

NCT00418574

Trial name or title	A Randomised,Double Blind, Placebo Controlled, Multicentre Trial of Abagovomab Maintenance Therapy in Patients With Epithelial Ovarian Cancer After Complete Response to First Line Chemotherapy
Methods	Randomised Placebo Controlled trial
Participants	870 ovarian cancer patients with complete clinical response to primary therapy
Interventions	s.c. monoclonal antibody targeting CA-125 (abagovomab)
Outcomes	Survival safety Immune responses
Starting date	December 2006
Contact information	
Notes	

NCT00437502

Trial name or title	A Phase I Study of Ovarian Cancer Peptides Plus GM-CSF and Adjuvant (Montanide ISA-51) as Consolidation Following Optimal Debulking and Systemic Chemotherapy for Women With Advanced Stage Ovarian, Tubal, or Peritoneal Cancer
Methods	Phase I study
Participants	18 stage III/IV ovarian cancer patients with complete clinical response to primary therapy
Interventions	s.c. ovarian cancer peptides plus GM-CSF
Outcomes	Safety Immune Responses Survival
Starting date	unknownnown
Contact information	
Notes	

NCT00585845

Trial name or title	A Phase 1, Open-Label, Dose-Escalation, Multiple Dose Study of the Safety, Tolerability, and Immune Response of CRS-207 in Adult Subjects With Selected Advanced Solid Tumors Who Have Failed or Who Are Not Candidates for Standard Treatment
Methods	Phase I study
Participants	17
Interventions	i.v. Live-attenuated Listeria monocytogenes expressing human Mesothelin i.v.
Outcomes	Dose-limiting toxicities
Starting date	December 2007
Contact information	
Notes	Study completion February 2009. No published records available

NCT00616941

Trial name or title	A Phase I Study of NY-ESO-1 Overlapping Peptides (OLP4) With or Without Immunoadjuvants Montanide and Poly-ICLC Vaccination of Epithelial Ovarian Cancer (EOC), Fallopian Tube, or Primary Peritoneal Cancer Patients in Second or Third Remission
Methods	Phase I

NCT00616941 (*Continued*)

Participants	26 stage II-IV ovarian cancer patients in second or third complete clinical remission
Interventions	s.c. NY-ESO-1 OLP4 alone, with Montanide or with Montanide and Poly-ICLC
Outcomes	Safety Immune Responses
Starting date	August 2008
Contact information	
Notes	

NCT00648102

Trial name or title	A Phase I, Open-Label, Dose-Escalation, Multidose Study of CDX-1307, a Mannose Receptor-Targeted hCG-β Vaccine, in Patients With Incurable Locally Advanced or Metastatic Breast, Colorectal, Pancreatic, Bladder and Ovarian Cancer
Methods	Phase I study
Participants	26 patients with incurable, metastatic or locally advanced breast, colorectal, pancreatic, bladder or ovarian cancer
Interventions	i.v. CDX-1307 (a fusion protein composed of a mannose receptor -specific immunoglobulin human monoclonal antibody and the hCG-β antigen)
Outcomes	Safety Clinical Responses
Starting date	January 2006
Contact information	
Notes	

NCT00693342

Trial name or title	A Randomized Phase III Trial in Patients With Epithelial Ovarian, Fallopian Tube or Peritoneal Cancer With a Polyvalent Vaccine-KLH Conjugate + OPT-821 versus OPT-821
Methods	Randomised phase III trial
Participants	164 ovarian cancer patients in second or third complete clinical remission
Interventions	s.c. polyvalent antigen-KLH conjugate vaccine in combination with s.c. OPT-821, or s.c. OPT-821

NCT00693342 (*Continued*)

Outcomes	Survival Safety Immune responses
Starting date	August 2008
Contact information	
Notes	possibly same study as NCT00857545

NCT00709462

Trial name or title	A Phase I, Open-Label, Dose-Escalation, Multidose Study of CDX-1307, a Mannose Receptor-Targeted hCG-β Vaccine, in Patients With Incurable Breast, Colorectal, Pancreatic, Ovarian or Bladder Cancer (CDX-1307-01)
Methods	Phase I study
Participants	48 patients with breast, colorectal, pancreatic, ovarian or bladder cancer without therapeutic options
Interventions	i.d. CDX-1307 (a fusion protein composed of a mannose receptor -specific immunoglobulin human monoclonal antibody and the hCG-β antigen)
Outcomes	safety / dose-limiting toxicity immune responses clinical responses survival
Starting date	March 2004
Contact information	
Notes	

NCT00803569

Trial name or title	Phase I Study of ALVAC(2)-NY-ESO-1(M)/TRICOM in Patients With Epithelial Ovarian, Fallopian Tube or Primary Peritoneal Carcinoma Whose Tumors Express NY-ESO-1 or LAGE-1 Antigen
Methods	Phase I
Participants	12 stage II-IV ovarian cancer patients with complete response to primary or secondary (chemo)therapy
Interventions	s.c. ALVAC(2)-NY-ESO-1(M)/TRICOM vaccine plus s.c. GM-CSF

NCT00803569 (*Continued*)

Outcomes	Safety Tumor responses Immune responses
Starting date	November 2008
Contact information	
Notes	

NCT00844506

Trial name or title	p53 Synthetic Long Peptides Vaccine With Cyclophosphamide for Ovarian Cancer a Phase II Trial
Methods	Uncontrolled phase II study
Participants	19 ovarian cancer patients with (bio-chemically) recurrent disease after prior therapy
Interventions	s.c. p53 synthetic long peptide vaccine / i.v. cyclophosphamide adjuvant: Montanide ISA51
Outcomes	Clinical responses Immune responses Safety
Starting date	October 2008
Contact information	
Notes	

NCT00857545

Trial name or title	A Phase III Randomized, Double-Blind Trial of a Polyvalent Vaccine-KLH Conjugate (NSC 748933) + OPT-821 versus OPT-821 in Patients With Epithelial Ovarian, Fallopian Tube, or Peritoneal Cancer Who Are in Second or Third Complete Remission
Methods	Randomized phase III study
Participants	164 stage II-IV ovarian cancer patient in second or third clinical remission
Interventions	s.c. polyvalent antigen-KLH conjugate vaccine and s.c. immunological adjuvant OPT-821, or s.c. OPT-821
Outcomes	Surviva Safety Immune Responses

NCT00857545 (*Continued*)

Starting date	January 2009
Contact information	
Notes	possibly same study as NCT00693342

NCT00887016

Trial name or title	Open Label Phase I Study to Evaluate the Safety and Tolerability of Vaccine (GI-6207) Consisting of Whole, Heat-Killed Recombinant Saccharomyces Cerevisiae Genetically Modified to Express CEA Protein in Adults With Metastatic CEA-Expressing Carcinoma
Methods	Phase I study
Participants	28 CEA-overexpressing cancer patients without therapeutic options
Interventions	Whole, Heat-Killed Recombinant Saccharomyces Cerevisiae Genetically Modified to Express CEA Protein
Outcomes	Safety Immune Responses Clinical responses Survival
Starting date	March 2009
Contact information	
Notes	

NCT00887796

Trial name or title	A Phase I Clinical Trial of NY-ESO-1 Protein Immunization in Combination With 5-AZA-2'-Deoxycytidine (Decitabine) in Patients Receiving Liposomal Doxorubicin for Recurrent Epithelial Ovarian or Primary Peritoneal Carcinoma
Methods	Phase I
Participants	18 ovarian cancer patients with recurrent disease
Interventions	decitabine in combination with NY-ESO-1 peptide vaccine (emulsified with incomplete Freund's adjuvant and sargramostim [GM-CSF]) and pegylated liposomal doxorubicin hydrochloride
Outcomes	Toxicity Immune Responses Survival
Starting date	April 2009

NCT00887796 (*Continued*)

Contact information	
Notes	

DATA AND ANALYSES

This review has no analyses.

ADDITIONAL TABLES

Table 1. Study Report Quality Assessment for non-randomised, non-controlled studies

Item	Question	Evaluation
1. a. b. c.	**Sample Definition and Selection** Are the inclusion and exclusion criteria clearly defined? Is the study population a representative selection of the true population? Are baseline characteristics adequately described?	Yes No Yes No Yes No
2 a. b.	**Interventions** Are the interventions clearly defined (type of vaccine, antigen, adjuvant, route of vaccination and vaccination schedule)? Did patients receive concurrent / concomitant treatment with immunomodulatory effects?	Yes No Yes No
3 a. b. c.	**Outcomes** Are the selected outcome measures clearly specified? Are the outcome measures relevant? Are the outcome measures clearly reported?	Yes No Yes No Yes No
4. a. b. c.	**Statistical Analysis** Is there an adequate rationale for the number of patients included? Is there an adequate description of withdrawal / exclusion of patients during the study? Is the presentation of the results adequate?	Yes No Yes No Yes No

Table 2. Overview of included studies

Study	Design	N	Disease status	Target antigen	Type of intervention
Berek 2001	RCT	252	NED after primary surgery and chemotherapy	CA-125	antibody versus placebo
Berek 2004	RCT	145	NED after primary surgery and chemotherapy	CA-125	antibody versus placebo

Table 2. Overview of included studies (*Continued*)

Berek 2009	RCT	317	NED after primary surgery and chemotherapy	CA-125	antibody versus placebo
Braly 2009	RCT	40	NED or ED after primary surgery	CA-125	antibody (concurrent or delayed with standard chemotherapy)
Brossart 2000	uncontrolled phase I/II	3	residual or recurrent disease	Her-2/Neu or MUC-1	peptide-pulsed dendritic cells
Chianese-Bullock 2008	uncontrolled phase I	9	NED / ED or recurrence after primary therapy	FBP, Her-2/Neu, MAGE-A1	multi-peptide vaccine
Chu 2008	RCT	14	NED after primary surgery and chemotherapy	Her-2/Neu, hTERT, PADRE	peptide-pulsed dendritic cells (alone or after single dose of cyclophosphamide)
Diefenbach 2008	uncontrolled phase I	9	NED after primary surgery and chemotherapy	NY-ESO-1	short peptide
Ehlen 2005	uncontrolled phase II	13	measurable recurrent disease	CA-125	antibody
Freedman 1998	RCT	30	unknown	Sialyl-Tn	KLH conjugate
Gordon 2004	uncontrolled phase II	20	recurrent disease	CA-125	antibody
Gulley 2008	uncontrolled phase I/II	3	progressive disease after standard chemotherapy	CEA, MUC1	recombinant virus
Herrin 2007	RCT	21	NED after prior therapy for primary or recurrent disease	p53	short peptide versus peptide-pulsed dendritic cells
Leffers 2009a	uncontrolled phase II	20	recurrent disease	p53	long peptides
Ma 2002	uncontrolled	4	unknown	CA-125	antibody
MacLean 1992	uncontrolled phase I	10	residual or recurrent disease	Thomson Friedenreich	KLH conjugate
MacLean 1996	uncontrolled phase II	34	residual or recurrent disease	Sialyl-Tn	KLH conjugate

Table 2. Overview of included studies (*Continued*)

Method 2002	RCT	102	unknown	CA-125	antibody (2 vs 3 vs 6 gifts)
Möbus 2003	retrospective uncontrolled	44	recurrent disease after primary therapy	CA-125	antibody
Mohebtash 2009	uncontrolled	17	metastatic disease	CEA, MUC1	recombinant virus
Nicholson 2004	uncontrolled phase I	26	residual disease after primary therapy or 2nd complete remission	MUC1	antibody
Nishikawa 2006	uncontrolled phase II	4	unknown	NY-ESO-1	short peptide
Noujaim 2001	retrospective uncontrolled	184	recurrent disease	CA-125	antibody
Odunsi 2007	uncontrolled phase I	18	NED or ED after chemotherapy for primary or recurrent disease	NY-ESO-1	short peptide
Odunsi 2007a	uncontrolled phase I/II	19	NED after primary therapy	NY-ESO-1	recombinant virus
Pfisterer 2006	uncontrolled phase I	36	unknown	CA-125	antibody
Reinartz 2004	uncontrolled phase Ib/II	119	unknown	CA-125	antibody
Sabbatini 2000	uncontrolled phase I	25	NED after chemotherapy for primary or recurrent disease	MUC1	KLH conjugate
Sabbatini 2006	RCT	42	NED or ED (<2cm) after chemotherapy for recurrent disease	CA-125	antibody (intramuscular versus subcutaneous)
Sabbatini 2007	uncontrolled phase I/II	11	NED after chemotherapy for primary or recurrent disease	GM2, Globo-H, Lewis Y, Tn-MUC1, Tn(c), sTN (c), TF(c)	heptavalent KLH conjugate
Sandmaier 1999	uncontrolled phase II	7	unknown	Sialyl-Tn	KLH conjugate
Schultes 1998	retrospective uncontrolled	75	unknown	CA-125	antibody

Table 2. Overview of included studies (*Continued*)

Ströhlein 2009	uncontrolled phase I	2	progressive disease	EpCAM or Her-2/Neu	trifunctional antibody
Tsuda 2004	uncontrolled phase I/II	7	NED or ED	patient-tailored cocktail	multi-peptide vaccine
van Zanten-Przybysz 2002	uncontrolled phase I/II	5	residual or recurrent disease after prior chemotherapy	membrane folate receptor	antibody
Wagner 1993	retrospective uncontrolled	58	unknown	CA-125	antibody

Table 3. Assessment of randomised controlled trial quality according to Delphi Checklist

	N	randomisation	concealed treatment allocation	groups similar at baseline	eligibility criteria specified	outcome assessor blinded	caregiver blinded	patient blinded	point estimates and measures of variability	intention-to-treat analysis	additional comment
Berek 2001	252	yes	not reported	yes	not reported	yes	yes	yes	no	not reported	abstract
Berek 2004	145	yes	not reported	yes	yes	yes	not reported	not reported	yes	yes	full text
Berek 2009	371	yes	yes	yes	yes	yes	yes	yes	yes	not reported	full text
Braly 2009	40	yes	not reported	no	no	not reported	no	no	yes	not reported	full text
Chu 2008	14	yes	not reported	not reported	not reported	not reported	no	no	yes	not reported	abstract
Freedman 1998	30	yes	not reported	not reported	not reported	yes	not reported	yes	yes	not reported	abstract
Herrin 2007	21	yes	not reported	not reported	not reported	not reported	no	no	no	not reported	abstract
Method 2002	102	yes	not reported	yes	not reported	not reported	no	no	no	not reported	abstract

Table 3. Assessment of randomised controlled trial quality according to Delphi Checklist (*Continued*)

Sabbatini 2006	42	yes	not reported	not reported	yes	not reported	no	no	yes	not reported	full text

Table 4. Assessment of study report quality of non-randomised (un)controlled studies

	N	Clear definition of inclusion/ exclusion criteria	Representative of true population	Baseline characteristics adequately described	Interventions clearly described	Concomitant / concurrent immunomodulatory treatment	Outcome measures clearly specified	Outcome measures relevant	Outcome measures clearly reported	Adequate rationale for number of patients	Adequate description of exclusion / withdrawal	Adequate presentation of results
Brossart 2000	3	yes	unknown	no	yes	unknown-nown	yes	yes	yes	no	no	no
Chianese-Bullock 2008	9	yes	no	yes	yes	unknown-nown	yes	yes	yes	no	yes	no
Diefenbach 2008	9	yes	no	yes	yes	no	yes	yes	yes	no	yes	yes
Ehlen 2005	13	yes	yes	yes	yes	unknown-nown	yes	yes	yes	no	yes	yes
Gulley 2008	3	yes	unknown	no	yes	unknown-nown	yes	yes	yes	no	yes	no
Herrin 2007	20	yes	yes	yes	yes	yes	yes	yes	yes	no	no	yes
Leffers 2009a	20	yes	unknown	yes	yes	no	yes	yes	yes	yes	yes	yes
Ma 2002	4	no	unknown	no	no	unknown	no	no	no	no	no	no

Table 4. Assessment of study report quality of non-randomised (un)controlled studies (*Continued*)

MacLean 1992	10	no	unknown	no	yes	yes	yes	yes	yes	no	no	yes
MacLean 1996	34	yes	unknown	no	yes	yes	no	yes	no	no	yes	no
Möbus 2003	44	yes	yes	yes	yes	yes	no	yes	yes	no	no	yes
Mohebtash 2009	17	no	unknown	no	yes	unknown	no	yes	no	no	no	no
Nicholson 2004	26	yes	unknown	no	yes	unknown	yes	yes	yes	no	yes	yes
Nishikaw 2006	4	no	unknown	no	no	unknown	yes	yes	yes	no	no	no
Noujaim 2001	184	yes	yes	yes	no	unknown	yes	yes	yes	no	no	yes
Odunsi 2007	18	no	no	yes	yes	unknown	no	yes	yes	no	unknown	yes
Odunsi 2007a	19	no	unknown	no	yes	unknown	no	yes	no	no	no	no
Pfisterer 2006	36	yes	unknown	no	yes	unknown	yes	yes	yes	no	yes	yes
Reinartz 2004	119	yes	unknown	no	yes	no	yes	yes	yes	no	no	yes
Sabbatini 2000	25	yes	yes	yes	yes	unknown	no	yes	yes	no	yes	yes
Sabbatini 2007	11	yes	unknown	yes	yes	unknown	yes	yes	yes	yes	yes	no
Sandmaier 1999	7	yes	unknown	no	yes	no	no	yes	yes	no	yes	yes

Table 4. Assessment of study report quality of non-randomised (un)controlled studies (*Continued*)

Schultes 1998	75	no	unknown	no	yes	unknown	no	yes	yes	no	no	yes
Ströhlein 2009	2	yes	no	no	yes	unknown	yes	yes	yes	no	yes	yes
Tsuda 2004	5	yes	no	no	yes	no	yes	yes	no	no	yes	no
van Zanten-Przybysz 2002	5	yes	no	yes	yes	unknown	yes	yes	yes	no	yes	yes
Wagner 1993	58	no	unknown	no	yes	unknown	no	yes	no	no	no	no

unknown - unknownnown

Table 5. Evaluation of clinical responses to immunotherapy

	n	analysed	method	CA-125		tumour		overall conclusion
				response definition	results	definition for tumour response	results	
Berek 2001	252	no						
Berek 2004	145	no						
Berek 2009	371	no						
Braly 2009	18/22	yes	unknown		yes	unknown		cCR 15x / 18x
Brossart 2000	3	yes	unknown					2x SD, 1x PD
Chianese-Bullock 2008	9	yes	both	unknown		unknown		1x NED, 8x PD

Table 5. Evaluation of clinical responses to immunotherapy (*Continued*)

Chu 2008	14	yes	unknown					3x PD, 7x NED
Diefenbach 2008	9	yes	both	unknown		unknown		not reported
Ehlen 2005	13	yes	both	decrease >15% (); <15% change (=) stable; >15% increase ()	4x , 1x =, 6x	unknown		3x SD, 10x PD
Freedman 1998	30	yes	unknown					18x SD, 10x PD
Gordon 2004	20	yes	both	unknown	6x	unknown		2x NED, 2x CR, 1x PR, 1x SD, 9x PD
Gulley 2008	3	yes	both	unknown		unknown		not reported
Herrin 2007	21	yes	unknown					8x PD, 3x NED
Leffers 2009a	20	yes	both	GCIG	not reported	RECIST	not reported	2x SD, 18x PD
Ma 2002	4	no						
MacLean 1992	10	yes	unknown					3x SD, 7x PD
MacLean 1996	34	no						
Method 2002	102	yes	unknown					not reported
Möbus 2003	44	no						
Mohebtash 2009	17	no						
Nicholson 2004	26	yes	CA-125	unknown				21x PD, 1x SD, 1x l.f.u., 3x unknown

Table 5. Evaluation of clinical responses to immunotherapy (*Continued*)

Nishikawa 2006	4	no						
Noujaim 2001	184	no						
Odunsi 2007	18	yes	tumour			unknown		1x CR, 17x unknown
Odunsi 2007a	19	no						
Pfisterer 2006	36	no						
Reinartz 2004	119	yes	tumour			WHO		not reported
Sabbatini 2000	25	no						
Sabbatini 2006	42	yes	both	unknown		unknown		12x SD, 21x PD, 9x withdrawal (6x PD)
Sabbatini 2007	11	no						
Sandmaier 1999	7	no						
Schultes 1998	75	no						
Ströhlein 2009	2	yes	both	unknown		unknown		1x PD, 1x PR or SD
Tsuda 2004	5	yes	both	unknown		WHO		4x PD, 1x SD
van Zanten-Przybysz 2002	5	yes	both	unknown	1x , 1x =, 1x , 2x unknown	unknown	1x NED, 1x SD, 2x PD, 1x unknown	3xPD, 2xSD
Wagner 1993	58	yes	CA-125	unknown				not reported

l.f.u. - lost in follow-up; cCR - complete clinical remission; CR - complete response; PR - partial response; SD - stable disease; PD - progressive disease; NED - no evidence of disease

Table 6. Definitions and results of survival analysis in antigen-specific antibody studies

Study	analysed	definition	results
Berek 2001	yes	time to relapse	NS: median TTR placebo 11.3, robust HAMA 16.4, and robust Ab2 18.9 months
Berek 2004	yes	time to relapse / overall survival	NS: TTR oregovomab 24.0 vs. placebo 10. 8 months (HR 0.543, 95%CI 0.287-1.025) ; OS 57.5 oregovomab vs. 48.6 placebo (HR 0.72, 95%C.I. 0.41-1.25)
Berek 2009	yes	time to relapse (randomisation to relapse)	NS: median TTR oregovomab 10.3 months vs placebo 12.9 months
Braly 2009	yes	progression free survival	NS: median PFS simultaneous administration 17.9 months vs. delayed administration 16.1 months
Ehlen 2005	yes	time to progression / survival (first dose to death)	TTP median 8.4 weeks (range 2-61 weeks); survival 37 weeks (range 11-110)
Gordon 2004	yes	time to progression / survival (first dose to death)	TTP median 11 weeks (T-cells responders vs non-responders p<0.0001 HR 0.150, 95%CI 0.006-0.168); survival median 70.4 weeks (T-cell responders vs non-responders P<0.002 HR 0.157, 95%CI 0.009-0.347)
Ma 2002	no		
Method 2002	no		
Möbus 2003	yes	survival (first dose to death) / overall survival (diagnosis to death)	survival median 16.8 months 95% CI 10. 3-22.6 (Ab3 responders vs non-responders 18.2 vs 13.1, p=0.0896; HAMA responders vs non-responders 22.6 months vs 7.6 months, p=0.0016); overall survival median 34.4 months
Nicholson 2004	no		
Noujaim 2001	yes	survival (first dose to death)	median survival & 3-year survival: Ab3 responders vs non-responders 22.9 vs 13.5 months, p=0.0089 ? 38% vs 8%; T-cell responders vs non-responders (n = 16) >84 vs 13.2 months, p=0.0202 ? 75% vs 0%
Pfisterer 2006	no		

Table 6. Definitions and results of survival analysis in antigen-specific antibody studies (*Continued*)

Reinartz 2004	yes	survival (first dose to death)	median survival 19.4 months, Ab3 responders vs non-responders: 23.4 vs 4.9 months, p<0.0001
Sabbatini 2006	yes	time to progression	TTP: 4 months (95%CI 3-5 months)
Schultes 1998	yes	overall survival (diagnosis to death)	median OS: robust Ab3 responders vs non-robust responders 49 vs 38 months , p=0.0029; Ab2 robust vs non-robust responders 30.0 vs 44.0 months, p=0.0475
Ströhlein 2009	yes	overall survival	not described separately for ovarian cancer patients
van Zanten-Przybysz 2002	yes	survival (first dose to death)	median survival 22.0 months
Wagner 1993	yes	not described	survival robust Ab2 vs non-robust Ab2 responders NS

Table 7. Definitions and results of survival analysis in other antigen-specific immunotherapy studies

Study	analysed	definition	results
Brossart 2000	no		
Chianese-Bullock 2008	no		
Chu 2008	no		
Diefenbach 2008	yes	time to progression (last chemo to relapse)	median TTP 13.0 months (95%CI 11.2 - not reached)
Freedman 1998	yes	progression free interval; survival	median PFI 4 months (95%CI 1.9-7.6); median survival 13.3. months (95%CI 1.5-30.8)
Gulley 2008	yes	progression free survival; overall survival	PFS: 9, 18, 19^{+} months; OS: 6, 19^{+}, 21 months
Herrin 2007	yes	progression free survival; overall survival	mean PFS 5 months; mean OS SQ vs. IV 70.4 vs. 72.9 months
Leffers 2009a	no		
MacLean 1996	yes	survival (trial entry to death)	median survival 12.7 months
MacLean 1992	no		

Table 7. Definitions and results of survival analysis in other antigen-specific immunotherapy studies (*Continued*)

Mohebtash 2009	yes	time to progression	median TTP 2 months (range 1-36)
Nishikawa 2006	no		
Odunsi 2007	yes	time to progression (first vaccination to relapse)	median TTP 19.0 months (95% CI 9.0 - not reached)
Odunsi 2007a	yes	disease free survival	median DFS 19.9 months
Sabbatini 2000	yes	time to progression (trial entry to relapse)	median TTP 6 months (range 2-17)
Sabbatini 2007	yes	time to progression (first vaccination to relapse)	median TTP 4.2 months (95% CI 2.7-8.5)
Sandmaier 1999	no		
Tsuda 2004	no		

TTR - time to relapse; PFI - progression free interval; PFS - progression free survival; DFS - disease free survival; CI - confidence interval; SQ - subcutaneous; IV - intravenous

Table 8. Definitions and results of anti-idiotypic (Ab2) humoral responses in antigen-specific monoclonal antibody studies

Study	N	Dose	target antigen	analysed	positive if:	% positive	robust if:	% robust
Berek 2001	252	2mg	CA-125	no	>50ng/ml	63%	>100ng/ml	
Berek 2004	145	2mg	CA-125	no			>100ng/ml	67%
Berek 2009	371	2mg	CA-125	no	unknown	n.r.	unknown	n.r.
Braly 2009	40	unknown	CA-125	yes			>100ng/ml	94% vs 74%
Ehlen 2005	13	2mg	CA-125	yes	>50ng/ml	45%		
Gordon 2004	20	2mg	CA-125	yes	>50ng/ml		>100ng/ml	79%
Ma 2002	4	unknown	CA-125	no				
Method 2002	102	2mg	CA-125	no			>100ng/ml	13% vs 31% vs 67%
Möbus 2003	44	2mg	CA-125	yes			>50ng/ml	77%

Table 8. Definitions and results of anti-idiotypic (Ab2) humoral responses in antigen-specific monoclonal antibody studies (*Continued*)

Nicholson 2004	26	25mg	MUC1	yes	unknown	100%		
Noujaim 2001	184	2mg	CA-125	yes				
Pfisterer 2006	36	2mg	CA-125	yes				
Reinartz 2004	119	2mg	CA-125	yes				
Sabbatini 2006	42	2mg/0.2mg	CA-125	yes				
Schultes 1998	75	2mg	CA-125	yes	>50ng/ml	64%	>250ng/ml	
Ströhlein 2009	2	10/20/40μg 10/40/80μg	EpCAM Her2/Neu	no				
van Zanten-Przybysz 2002	5	50mg	membrane folate receptor	no				
Wagner 1993	58	1mg	CA-125	no	>0u/l	64%	>10u/l	32%

n.r. - not reported; *increased titers in patients treated with 90-Y-muHMFG1 (n = 208) compared to standard treatment (n = 199)

Table 9. Definitions and results of anti-anti-idiotypic (Ab3) humoral responses in antigen-specific antibody studies

Study	N	Dose	target antigen	analysed	positive if:	% positive	robust if:	% robust
Berek 2001	252	2mg	CA-125	no				
Berek 2004	145	2mg	CA-125	no				
Berek 2009	371	2mg	CA-125	no				
Braly 2009	40	unknown	CA-125	no				
Ehlen 2005	13	2mg	CA-125	yes	>100ng/ml		>3x baseline	0%
Gordon 2004	20	2mg	CA-125	yes	>100ng/ml		>3x baseline	10,5%

Table 9. Definitions and results of anti-anti-idiotypic (Ab3) humoral responses in antigen-specific antibody studies (*Continued*)

Ma 2002	4	unknown	CA-125	no				
Method 2002	102	2mg	CA-125	no				
Möbus 2003	44	2mg	CA-125	yes			>3x baseline	28%
Nicholson 2004	26	25mg	MUC1	yes	>0.015ug/ml	38%		
Noujaim 2001	184	2mg	CA-125	yes			>3x baseline	43%
Pfisterer 2006	36	2mg	CA-125	yes	>1000ng/ml	L vs S: 100% vs 100%		
Reinartz 2004	119	2mg	CA-125	yes	>1000u/ml	68%		
Sabbatini 2006	42	2mg/0.2mg	CA-125	yes	>1000u/ml	100%		
Schultes 1998	75	2mg	CA-125	yes	>200ng/ml	24%	>3x baseline	
Ströhlein 2009	2	10/20/40μg 10/40/80μg	EpCAM Her2/Neu	no				
van Zanten-Przybysz 2002	5	50mg	membrane folate receptor	no				
Wagner 1993	58	1mg	CA-125	no				

Table 10. Definitions and results of humoral response evaluation in other antigen-specific immunotherapy studies

Study	N	target antigen(s)	analyzed	assay	positive if:	% positive
Brossart 2000	3	Her-2/Neu, MUC1	no			
Chianese-Bullock 2008	9	FBP, Her-2/Neu, MAGE-A1	no			
Chu 2008	14	Her-2/Neu, hTERT, PADRE	no			

Table 10. Definitions and results of humoral response evaluation in other antigen-specific immunotherapy studies (*Continued*)

Diefenbach 2008	9	NY-ESO-1	yes	ELISA	>100	0%
Gulley 2008	3	CEA, MUC1	no			
Freedman 1998	30	Sialyl Tn	no			
Herrin 2007	21	p53	no			
Leffers 2009a	20	p53	yes	unknown	unknown	pre-imm: 40%, post-imm: 45%
MacLean 1992	10	Thomson Friedenreich	yes	ELISA	unknown	80% IgA, 90% IgM, 90% IgG, 0% IgE
MacLean 1996	34	Sialyl Tn	yes	ELISA	unknown	96%
Mohebtash 2009	17	MUC1, CEA	no			
Nishikawa 2006	4	NY-ESO-1	no			
Odunsi 2007	18	NY-ESO-1	yes	ELISA	unknown	22%
Odunsi 2007a	19	NY-ESO-1	yes	ELISA	unknown	38%
Sabbatini 2000	25	Lewis Y	yes	ELISA	unknown	67%
Sabbatini 2007	11	GM2, Globo-H, Lewis Y, Tn-MUC1, Tn(c) sTN (c), TF(c)	yes	ELISA	negative to ≥ 1:40 or 8-fold increase	89% ≥3 antigens; 22% GM2, 33% Globo-H, 11% Lewis Y, 100% Tn-MUC1, 44% Tn(c), 44% sTN(c), 78% TF(c)
Sandmaier 1999	7	Sialyl Tn	yes	ELISA	≥1:20	100% IgM, 80% IgG
Tsuda 2004	5	patient-tailored cocktail	yes	ELISA	unknown	67%

Table 11. Definitions and results of cellular responses in antigen-specific antibody studies

Study	N	Dose	target antigen	analysed	assay	positive if:	% positive
Berek 2001	252	2mg	CA-125	no			
Berek 2004	145	2mg	CA-125	no			
Berek 2009	371	2mg	CA-125	no			

Table 11. Definitions and results of cellular responses in antigen-specific antibody studies (*Continued*)

Braly 2009	40	unk	CA-125	yes	ELISPOT	permutation test	44% vs. 21%
Ehlen 2005	13	2mg	CA-125	yes	ELISPOT	permutation test	n = 4 CA-125: 75%; n = 3 oregovomab 67%
Gordon 2004	20	2mg	CA-125	yes	ELISPOT	permutation test	n = 18 CA-125: 39%; n = 18 oregovomab 50%; n = 8 autologous tumour cells 63%
Ma 2002	4	unk	CA-125	yes	proliferation assay	unknown	n = 4: 50%
Method 2002	102	2mg	CA-125	yes	ELISPOT	NR	NR
Möbus 2003	44	2mg	CA-125	no			
Nicholson 2004	26	25mg	MUC1	no			
Noujaim 2001	184	2mg	CA-125	yes	proliferation assay / cytokine ELISA	proliferation assay: wilcoxon signed rank test; cytokine ELISA: unknown	n = 17 CA-125 53%; Th1 cytokines 41%, Th2 cytokines 94%
Pfisterer 2006	36	2mg	CA-125	yes	cytokine flow cytometry	>2-fold increase in IFN-γ expressing T-cells	L vs S: n = 12 vs 17, CD4: 58% vs 29%; CD8 75% vs 18%
Reinartz 2004	119	2mg	CA-125	no			
Sabbatini 2006	42	2mg/0.2mg	CA-125	yes	ELISPOT	spots experimental wells - control wells >20 & experimental wells/control wells >1.5x	n = 5: 80%
Schultes 1998	75	2mg	CA-125	no			
Ströhlein 2009	2	10/20/40μg 10/40/80μg	EpCAM Her2/Neu	yes	IFN-γ secretion assay	unknown	EpCAM n = 1 (100%) Her2/Neu n = 1 (0%)

Table 11. Definitions and results of cellular responses in antigen-specific antibody studies (*Continued*)

van Zanten-Przybysz 2002	5	50mg	membrane folate receptor	yes	proliferation assay	unknown	0%
Wagner 1993	58	1mg	CA-125	yes	leukocyte migration inhibition assay	unknown	21%

NR - not reported

Table 12. Definitions and results of cellular responses in other antigen-specific immunotherapy studies

Study	N	target antigen(s)	analysed	assay	positive if:	% positive
Brossart 2000	3	Her-2/Neu, MUC1	yes	intracellular IFN-γ staining (CD8)	unknown	n = 1: Her-2/Neu 100%; n = 2 MUC1 50%
Chianese-Bullock 2008	9	FBP, Her-2/Neu, MAGE-A1	yes	ELISPOT (CD8)	unknown	n = 9: FBP 40%, Her-2/neu 83%, MAGE-A1 83%
Chu 2008	14	Her-2/Neu, hTERT, PADRE	yes	ELISPOT	unknown	n = 5: 100% hTERT, 60% Her-2/Neu
Diefenbach 2008	9	NY-ESO-1	yes	ELISPOT / Tetramer staining (CD8)	specific spots > 30 and >3x spots irrelevant control >0.1% tetramer positive CD8-cells	both assays n = 9: 67%
Freedman 1998	30	Sialyl Tn	no			
Gulley 2008	3	CEA, MUC1	yes	ELISPOT (CD8) / IFN-γ ELISA (CD4)	ELISPOT: $\geq$2-fold increase in IFN-γ secreting cells IFN-γ ELISA: unknown	n = 3: 100% CEA n = 3: 33% CEA
Herrin 2007	21	p53	yes	ELISPOT	unknown	n = 13 vs. 7: 69% vs. 71%
Leffers 2009a	20	p53	yes	ELISPOT / proliferation assay / intracellular IFN-γ staining (CD4/CD8)	ELISPOT: specific spots $\geq 10/10^5$ PBMC and $\geq$3x higher than before imm. proliferation: cpm > 1000/minute, SI$\geq$3	n = 18: 100% n = 17: 82% n = 5: CD8 0%, CD4 100%

Table 12. Definitions and results of cellular responses in other antigen-specific immunotherapy studies (*Continued*)

					and ≥2x higher than before imm intracellular staining: ≥3 higher than before imm.	
MacLean 1992	10	Sialyl Tn	no			
MacLean 1996	34	Thomson Friedenreich	no			
Mohebtash 2009	17	MUC1, CEA	no			
Nishikawa 2006	4	NY-ESO-1	yes	ELISPOT (CD4)	unknown	n = 4: 75%
Odunsi 2007	18	NY-ESO-1	yes	ELISPOT (CD4 / CD8)	ELISPOT: mean ± 3 SD	n = 18: CD4 - 83%; n = 9: CD8 - 33%
Odunsi 2007a	19	NY-ESO-1	yes	ELISPOT (CD4 / CD8)	unknown	n = 9: CD8 - 55%, CD4 ?
Sabbatini 2000	25	Lewis Y	no			
Sabbatini 2007	11	GM2, Globo-H, Lewis Y, Tn-MUC1, Tn(c) sTN (c), TF(c)	no			
Sandmaier 1999	7	Sialyl Tn	yes	proliferation assay*	>upper limit of normals (SI 2.35)	n = 4 50%
Tsuda 2004	5	patient-tailored cocktail	yes	IFN-γ ELISA	unclear	n = 2 after 6 vacc. 100%; n = 1 after 12 vacc. 100%

* as measured after at least three immunizations; SI - stimulation index; SD - standard deviation

Table 13. Definitions and results of human-anti-mouse antibody (HAMA) evaluation in antigen-specific antibody studies

Study	N	Dose	target antigen	analysed	positive if:	% positive	robust if:	% robust
Berek 2001	252	2mg	CA-125	yes			>5000ng/ml	51%
Berek 2004	145	2mg	CA-125	yes	>200ng/ml	unknown	>5000ng/ml	59%
Berek 2009	371	2mg	CA-125	yes	unknown	n.r.		

Table 13. Definitions and results of human-anti-mouse antibody (HAMA) evaluation in antigen-specific antibody studies (*Continued*)

Braly 2009	40	unk	CA-125	yes	unknown	SIM vs OWD: 100% vs 80%	>3000ng/ml	SIM vs OWD: 88% vs 74%
Ehlen 2005	13	2mg	CA-125	yes	>200ng/ml	100%	>5000ng/ml	58%
Gordon 2004	20	2mg	CA-125	yes	>200ng/ml	unknown	>5000ng/ml	79%
Ma 2002	4	unk	CA-125	no				
Method 2002	102	2mg	CA-125	yes	>200ng/ml	unknown	unknown	4% vs 36% vs 39%
Möbus 2003	44	2mg	CA-125	yes			>5000ng/ml	68%
Nicholson 2004	26	25mg	MUC1	no				
Noujaim 2001	184	2mg	CA-125	no				
Pfisterer 2006	36	2mg	CA-125	yes	>15ng/ml	L vs. S: 94% vs 100%		
Reinartz 2004	119	2mg	CA-125	yes	>100ng/ml	78%		
Sabbatini 2006	42	2mg/0.2mg	CA-125	yes	>100ng/ml	90%		
Schultes 1998	75	2mg	CA-125	yes	>200ng/ml	90%		
Ströhlein 2009	2	10/20/40μg 10/40/80μg	EpCAM Her2/Neu	yes	unknown	100% (n = 1)		
van Zanten-Przybysz 2002	5	50mg	membrane folate receptor	n.a.				
Wagner 1993	58	1mg	CA-125	no				

n.a. - not applicable; n.r. - not reported

APPENDICES

Appendix 1. PubMed search strategy

PubMed search
PubMed RCT search filter: 1. randomised controlled trial [pt] 2. controlled clinical trial [pt] 3. randomised [tiab] 4. placebo [tiab] 5. drug therapy [sh] 6. randomly [tiab] 7. trial [tiab] 8. groups [tiab] 9. #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 10. humans [mh] 11. #9 and #10 PubMed search for patient population: 12. ovary 13. ovarian 14. # 12 OR # 13 15. cancer OR carcinoma OR neoplasm OR tumor OR tumors OR tumour OR tumours OR malignan* 16. # 14 AND # 15 17. ovarian neoplasms [mh] 18. # 16 OR # 17 PubMed search for Intervention: 19. immunotherapy[tiab] 20. vaccination[tiab] 21. vaccine[tiab] 22. immunization[tiab] 23. active immunotherapy[mh] 24. cancer vaccines[mh] 25. #19 OR #20 OR #21 OR #22 OR #23 OR #24 26. antigen* OR tumor antigen OR tumour antigen 27. Antigens, Neoplasm [mh] 28. # 26 OR # 27 29. T cell OR T-cell OR T lymphocyte OR T-lymphocyte OR CD4-positive T-lymphocyte OR CD8-positive lymphocyte 30. T-lymphocytes [mh] 31. # 29 OR # 30 32. # 25 OR # 28 OR # 31 Search for all types of different trials: 33. # 18 AND # 32 (all trials) 34. #33 AND #10 (all human trials) 35. # 11 AND # 18 AND # 32 (RCT's only) *

Appendix 2. EMBASE search strategy

EMBASE search
1. 'crossover procedure'/exp
2. 'double-blind procedure'/exp
3. 'randomized controlled trial'/exp
4. 'single-blind procedure'/exp
5. random$ OR crossover$ OR 'cross over'$ OR cross AND over$ OR factorial$ OR placebo$ OR doubl$ adj blind$ OR singl$ adj blind$ OR allocat$ OR assign$ OR volunteer$
6. #1 OR #2 OR #3 OR #4 OR #5
7. 'ovary' OR 'ovarian' OR 'ovarium'
8. 'cancer' OR 'carcinoma' OR 'neoplasm' OR 'tumor' OR 'tumour' OR 'tumors' OR 'tumours' OR 'malignancy'
9. #7 AND #8
10. 'ovary tumor'/exp
11. #9 OR #10
12. 'active immunization'/exp
13. 'cancer immunization'/exp
14. 'cancer vaccine'/exp
15. 'vaccination' OR 'vaccine' OR 'immunization' OR 'immunisation' OR 'immunotherapy'
16. #12 OR #13 OR #14 OR #15
17. 'tumor antigen'/exp
18. 't cell' OR 't-cell' OR 't lymphocyte' OR 't-lymphocyte' OR 'cd4-positive t-lymphocyte' OR 'cd8-positive t-lymphocyte'
19. 't lymphocyte'/exp
20. #18 OR #19
21. #16 AND #17 AND #20
22. #11 AND #21 AND [humans]/lim

Appendix 3. CENTRAL search strategy

CENTRAL search
(ovary OR ovarian) AND ((cancer OR carcinoma OR neoplasm OR tumor OR tumors OR tumour OR tumours OR malignan*) OR (ovarian neoplasms))
and
(immunotherapy OR vaccination OR vaccine OR immunization OR active immunotherapyn OR cancer vaccines)
and
(antigen* OR tumor antigen OR tumour antigen) OR (Antigens Neoplasm)
and
(T cell OR T-cell OR T lymphocyte OR T-lymphocyte OR CD4-positive T-lymphocyte OR CD8-positive lymphocyte)

Appendix 4. Data extraction form

CRITICAL REVIEW & DATA EXTRACTION FORM
Review Title: Antigen-specific active immunotherapy for ovarian cancer
Date: …… Reviewer: ……
Study Title: …….

First Author	
Year of Publication	
Country of Publication	
Publication Type	Journal / Abstract / other (specify)

Study Characteristics*

	Study
Study inclusion criteria	
Study exclusion criteria	
Participants	· Total number of participants: …… · Number of patients with EOC: ……. · Age: o Median + range: …… o Mean + SD: …… · FIGO stage: …… · Histological tumor type: …… · Tumor grade: …… · Previous therapy: …… · Concurrent therapy: ……..
Trial intervention	· type of vaccine: …… · antigen used: …… · adjuvant used: ……. · route of vaccination: …… · vaccination schedule: …….

Outcomes

Trial	N + reason
Patients excluded during trial	
Patients lost to follow up	

Clinical responses	N
CA-125 levels according to GCIG definition	Decreasing: ……. Stable: …….. Progressing: …… Total: …….
Tumor response according to RECIST or WHO criteria	Complete remission: ……. Partial remission: …….. Stable disease: …….. Progressive disease: …….. Total: …….
Postimmunotherapy treatment	Administered: Yes ? No ? If yes: specify response to post immunotherapy treatment: Complete remission: ……. Partial remission: …….. Stable disease: …….. Progressive disease: …….. Total: …….
Survival	Information on survival available: Yes ? No ? If yes, specify: …… ……

Immunogenicity	
1. *Antigen-specific immunogenicity*	
Humoral responses	Observed Total Assay(s) used: ……

(*Continued*)

Cellular responses	Observed Total Assay(s) used: …… Separate information on cytotoxic T-lymphocytes and Thelper lymphocytes available: Yes ? No ? If yes, specify: ……
Vaccine or vector specific immunogenicity: Applicable Yes ? No ?	
Humoral responses	Observed Total Assay(s) used: ……
Cellular responses	Observed Total Assay(s) used: ……

Adverse events	
Type of AE's	· Local events (injection site): Yes ? No ? If yes, specify: …… · Systemic: Yes ? No ? If yes: Autoimmunity Yes ? No ? If yes, specify: …… Allergic reactions Yes ? No ? If yes, specify: …… Other Yes ? No ? If yes, specify: ……

Other

Contact with primary investigators	Clarify Methods ? Clarify Results ?
Notes	

WHAT'S NEW

Last assessed as up-to-date: 30 October 2009.

Date	Event	Description
27 March 2014	Amended	Contact details updated.

CONTRIBUTIONS OF AUTHORS

NL selected relevant studies, assessed study quality, extracted data and wrote the review. HWN selected relevant studies, assessed study quality and extracted data. TD and WH checked all rejected titles and resolved any disagreements on study selection and data extraction. HMB and BC provided statistical and methodological support. KM supported in writing the review as an expert in immunology.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- None, Not specified.

External sources

- None, Not specified.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

TD was added to the team. No further relevant differences between protocol and review.

INDEX TERMS

Medical Subject Headings (MeSH)

Antibodies, Monoclonal [therapeutic use]; CA-125 Antigen [immunology]; Clinical Trials, Phase I as Topic; Clinical Trials, Phase II as Topic; Immunotherapy, Active [*methods]; Ovarian Neoplasms [immunology; *therapy]; Randomized Controlled Trials as Topic

MeSH check words

Female; Humans